

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|---|--|-----------|--|
| (51) International Patent Classification ⁷ : C07D 401/12, 401/14, 409/14, 417/14, 235/28, 471/04, A61K 31/4184, 31/4439 | | A1 | (11) International Publication Number: WO 00/09498 |
| | | | (43) International Publication Date: 24 February 2000 (24.02.00) |
| (21) International Application Number: PCT/US99/18048 (22) International Filing Date: 9 August 1999 (09.08.99) (30) Priority Data: 09/131,481 10 August 1998 (10.08.98) US 09/364,381 29 July 1999 (29.07.99) US (71) Applicant: PARTNERSHIP OF MICHAEL E. GARST, GEORGE SACHS AND JAI MOO SHIN [US/US]; 2627 Raqueta, Newport Beach, CA 92660 (US). (72) Inventors: GARST, Michael, E.; 2627 Raqueta, Newport Beach, CA 92660 (US). SACHS, George; 17986 Boris Drive, Encino, CA 91316 (US). SHIN, Jai, Moo; 18833 Nau Avenue, Northridge, CA 91326 (US). (74) Agents: KLEIN, Howard, J. et al.; Klein & Szekeres, LLP, Suite 700, 4199 Campus Drive, Irvine, CA 92612 (US). | | | (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |
| (54) Title: PRODRUGS OF PROTON PUMP INHIBITORS | | | |
| (57) Abstract Prodrugs of the pyridyl methyl sulfinyl benzimidazole type proton pump inhibitor drugs have a hydrolyzable sulfinyl or arylsulfonyl group attached to the benzimidazole nitrogen, or include a group that forms a <i>Mannich</i> base with the benzimidazole nitrogen. The prodrugs of the invention hydrolyze under physiological conditions to provide the proton pump inhibitors with a half life measurable in hours, and are capable of providing sustained plasma concentrations of the proton pump inhibitor drugs for longer time than presently used drugs. The generation of the proton pump inhibitor drugs from the prodrugs of the invention under physiological conditions allows for more effective treatment of several diseases and conditions caused by gastric acid secretion. | | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | | | TR | Turkey |
| BG | Bulgaria | HU | Hungary | ML | Mali | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MN | Mongolia | UA | Ukraine |
| BR | Brazil | IL | Israel | MR | Mauritania | UG | Uganda |
| BY | Belarus | IS | Iceland | MW | Malawi | US | United States of America |
| CA | Canada | IT | Italy | MX | Mexico | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NE | Niger | VN | Viet Nam |
| CG | Congo | KE | Kenya | NL | Netherlands | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NO | Norway | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | NZ | New Zealand | | |
| CM | Cameroon | | | PL | Poland | | |
| CN | China | KR | Republic of Korea | PT | Portugal | | |
| CU | Cuba | KZ | Kazakstan | RO | Romania | | |
| CZ | Czech Republic | LC | Saint Lucia | RU | Russian Federation | | |
| DE | Germany | LI | Liechtenstein | SD | Sudan | | |
| DK | Denmark | LK | Sri Lanka | SE | Sweden | | |
| EE | Estonia | LR | Liberia | SG | Singapore | | |

PRODRUGS OF PROTON PUMP INHIBITORS

BACKGROUND OF THE INVENTION

3. Cross-reference to Related Application

The present application is a continuation-in-part of application serial number 09/131,481, filed on August 10, 1998.

2. Field of the Invention

The present invention is directed to prodrugs of proton pump inhibitors which are useful as anti-ulcer agents. More particularly, the present invention is directed to prodrugs that slowly hydrolyze to provide benzimidazole-type proton pump inhibitors which inhibit exogenously or endogenously gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases in mammals, including humans.

3. Brief Description of the Prior Art

Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in the United States Patent Nos. 4,045,563; 4,255,431; 4,628,098; 4,686,230; 4,758,579; 4,965,269; 5,021,433; 5,430,042 and 5,708,017. Generally speaking, the benzimidazole-type inhibitors of gastric acid secretion work by undergoing a rearrangement to form a thiophilic species which then covalently binds to gastric H,K-ATPase, the enzyme involved in the final step of proton production in the parietal cells, and thereby inhibits the enzyme. Compounds which inhibit the gastric H,K-ATPase enzyme are generally known in the field as "proton pump inhibitors" (PPI).

Some of the benzimidazole compounds capable of inhibiting the gastric H,K-ATPase enzyme have found substantial use as drugs in human medicine and are known under such names as LANSOPRAZOLE (United States Patent No. 4,628,098), OMEPRAZOLE (United States Patent Nos. 4,255,431 and 5,693,818), PANTOPRAZOLE (United States Patent No. 4,758,579), and RABEPRAZOLE (United States Patent No. 5,045,552). The diseases treated

1 by proton pump inhibitors and specifically by the four above-mentioned drugs
2 include peptic ulcer, heart burn, reflux esophagitis erosive esophagitis, non-
3 ulcer dyspepsia, infection by *Helicobacter pylori*, alrnyitis and asthma among
4 others.

5 Whereas the proton pump inhibitor type drugs represent substantial
6 advance in the field of human and veterinary medicine, they are not totally
7 without shortcomings or disadvantages. The shortcomings of the presently
8 used proton pump inhibitor (PPI) type drugs can be best explained by a more
9 detailed description of the mode of their action, the diseases or condition
10 against which they are employed and the circumstances of their application.
11 Thus, acid related diseases include but are not limited to erosive esophagitis,
12 esophageal reflux, gastric and duodenal ulcer, non-ulcer dyspepsia and
13 infection by *Helicobacter pylori*. Current therapy of all but the infection by *H.*
14 *pylori* bacteria involves treatment with drugs designed to suppress acid
15 secretion, one type of which are the above-mentioned proton pump inhibitors.

16 The presently used proton pump inhibitors are pyridyl methyl sulfinyl
17 benzimidazoles (or compounds of closely related structure) with a pK_a of 4.0
18 to 5.0. Their mechanism of action requires accumulation in the acidic space
19 of the parietal cell (secretory canaliculus, pH ca. 1.0) and subsequently
20 hydrogen ion catalyzed conversion to the reactive thiophilic species that is
21 capable of inhibiting the gastric ATPase, enzyme resulting in effective
22 inhibition of gastric secretion. Because of this mechanism the presently used
23 PPI type drugs require specialized gastro protection to remain active for
24 duodenal absorption. For this reason, and due to sensitivity to degradation in
25 the acid milieu of the stomach, oral formulations of the PPI drugs are usually
26 enteric coated. The need for enteric coating is a shortcoming because enteric
27 coating is expensive and moisture sensitive.

28 Because of the requirement for accumulation in the acid space of the

1 parietal cell, acid secretion is necessary for the efficacy of the PPI type drugs.
2 It was found that the plasma half life of these drugs is between 60 to 90
3 minutes. All acid pumps are not active at any one time, rather only about 75
4 % are active on the average during the time the drug is present in the blood
5 following oral administration. It was also found in medical experience that on
6 a currently used once-a-day oral administration therapy the maximal
7 inhibition of stimulated acid output is approximately 66 %. This is due to a
8 combination of the short plasma half life of the drug, to the limited number of
9 acid pumps active during presentation of the drug and to the turn-over of acid
10 pumps. In present practice it is not possible to control night time acid
11 secretion by evening therapy of oral administration because the drug is
12 dissipated from the plasma by the time acid secretion is established after
13 midnight. The ideal target for healing in acid related diseases and for
14 treatment of *H. pylori* infection (in conjunction with antibiotics), as well as for
15 relief of symptoms of non-ulcer dyspepsia would be full inhibition of acid
16 secretion. With the currently used PPI type drugs this is achieved only by
17 intravenous infusion; in case of the drug OMEPRAZOLE this requires
18 intravenous infusion of 8 mg per hour. Clearly, there is a need in the art for a
19 drug or drugs acting through the mechanism of PPI -type drugs which can
20 attain or approach full inhibition of acid secretion through oral therapy.

21 Because of the less than full inhibition of acid secretion and less than
22 24 hour inhibition through oral administration that is attained by the current
23 dosage forms of currently used PPI-type drugs, therapy for healing of gastric
24 and duodenal ulcerations is 4 to 8 weeks. This is in spite of the fact that the
25 generation time of surface cells of the esophagus, stomach and duodenum is
26 approximately 72 hours. Undoubtedly the presently observed prolonged
27 healing times with these drugs is due to inadequate acid suppression and acid
28 related damage. The foregoing underscores the need in the art for a drug or

1 drugs acting through the mechanism of PPI -type drugs which can attain or
2 approach full inhibition of acid secretion through oral therapy.

3 As further pertinent background to the present invention, applicants
4 note the concept of prodrugs which is well known in the art. Generally
5 speaking, prodrugs are derivatives of *per se* drugs, which after administration
6 undergo conversion to the physiologically active species. The conversion may
7 be spontaneous, such as hydrolysis in the physiological environment, or may
8 be enzyme catalyzed. From among the voluminous scientific literature
9 devoted to prodrugs in general, the foregoing examples are cited: **Design of**
10 **Prodrugs** (Bundgaard H. ed.) 1985 Elsevier Science Publishers B. V.
11 (Biomedical Division), Chapter 1; Design of Prodrugs: Bioreversible
12 derivatives for various functional groups and chemical entities (Hans
13 Bundgaard); *Bundgaard et al. Int. J. of Pharmaceutics* 22 (1984) 45 - 56
14 (Elsevier); *Bundgaard et al. Int. J. of Pharmaceutics* 29 (1986) 19 - 28
15 (Elsevier); *Bundgaard et al. J. Med. Chem.* 32 (1989) 2503 - 2507 **Chem.**
16 **Abstracts** 93, 137935y (*Bundgaard et al.*); **Chem. Abstracts** 95, 138493f
17 (*Bundgaard et al.*); **Chem. Abstracts** 95, 138592n (*Bundgaard et al.*);
18 **Chem. Abstracts** 110, 57664p (*Alminger et al.*); **Chem. Abstracts** 115,
19 64029s (*Buur et al.*); **Chem. Abstracts** 115, 189582y (*Hansen et al.*);
20 **Chem. Abstracts** 117, 14347q (*Bundgaard et al.*); **Chem. Abstracts** 117,
21 55790x (*Jensen et al.*); and **Chem. Abstracts** 123, 17593b (*Thomsen et al.*).

22 As far as the present inventors are aware, there are no prodrugs of the
23 proton pump inhibitors presently in use. However, several United States
24 patents describe compounds which can act as prodrugs of certain proton pump
25 inhibitors. Specifically, United States Patent No. 4,686,230 (*Rainer et al.*)
26 describes derivatives of pyridyl methyl sulfinyl benzimidazoles which include
27 a group designated "R₅" on one of the benzimidazole nitrogens. The "R₅"
28 group is expected to cleave under physiological condition, or under the

1 influence of an enzyme to provide the corresponding compound with a free N-
2 H bond (see column 3 of United States Patent No. 4,686,230). United States
3 Patent Nos. 5,021,433 (*Alminger et al.*), 4,045,563 (*Berntsson et al.*),
4 4,965,269 and (*Brändström et al.*) also describe pyridyl methyl sulfinyl
5 benzimidazoles where one of the nitrogens of the benzimidazole moiety bears
6 a substituent that cleaves under physiological or enzymatic conditions.

7 The present invention represents further advance in the art in that it
8 provides prodrugs of improved structure of the proton pump inhibitor type
9 drugs and provides proof of the suitability of the prodrugs of the invention for
10 use as prodrug of proton pump inhibitors, with improved efficacy in therapy of
11 acid related diseases due to prolongation of the presence of the proton pump
12 inhibitors in the body.

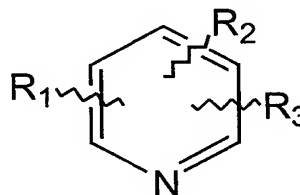
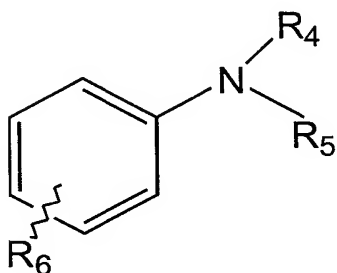
13 SUMMARY OF THE INVENTION

14 The present invention relates to compounds of **Formula 1**

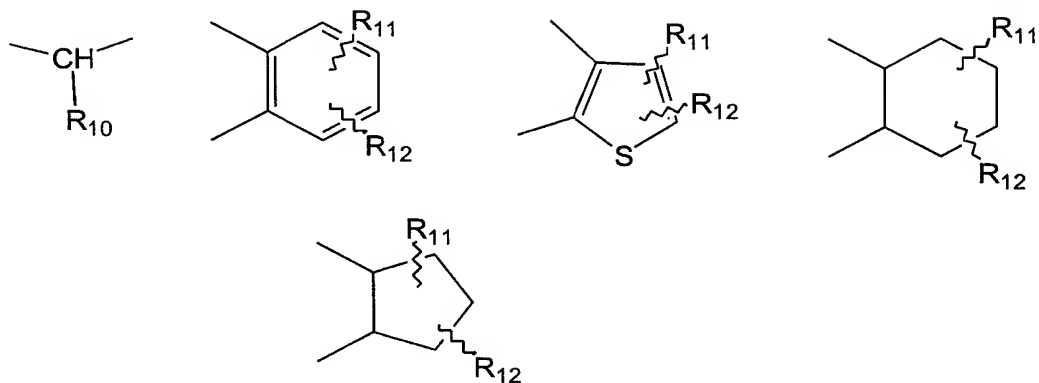


16 wherein

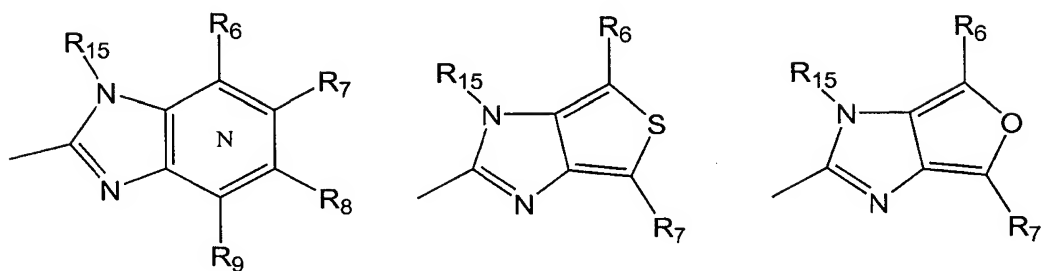
17 Het_1 is selected from the formulas shown below



X is selected from the formulas



and Het₂ is selected from the formulas



1 where N in the benzimidazole moiety means that one of the ring
2 carbons may be exchanged for an unsubstituted N atom;

3 R_1 , R_2 and R_3 are independently selected from hydrogen, alkyl of 1
4 to 10 carbons, fluoro substituted alkyl of 1 to 10 carbons, alkoxy of 1 to 10
5 carbons, fluoro substituted alkoxy of 1 to 10 carbons, alkylthio of 1 to 10
6 carbons, fluoro substituted alkylthio of 1 to 10 carbons, alkoxyalkoxy of 2 to
7 10 carbons, amino, alkylamino and dialkylamino each of the alkyl groups in
8 said alkylamino and dialkyl amino groups having 1 to 10 carbons, halogen,
9 phenyl, alkyl substituted phenyl, alkoxy substituted phenyl, phenylalkoxy,
10 each of the alkyl groups in said alkyl substituted phenyl, alkoxy substituted
11 phenyl and phenylalkoxy having 1 to 10 carbons, piperidino, morpholino or
12 two of the R_1 , R_2 and R_3 groups jointly forming a 5 or 6 membered ring
13 having 0 or 1 heteroatom selected from N, S and O;

14 R_4 and R_5 are independently selected from hydrogen, alkyl of 1 to 10
15 carbons, fluoro substituted alkyl of 1 to 10 carbons, phenylalkyl, naphthylalkyl
16 and heteroarylalkyl, alkyl in said phenylalkyl, naphthylalkyl and
17 heteroarylalkyl groups having 1 to 10 carbons;

18 R_6 is hydrogen, halogen, alkyl of 1 to 10 carbons, fluoro substituted
19 alkyl of 1 to 10 carbons, alkoxy having 1 to 10 carbons or fluoro substituted
20 alkoxy having 1 to 10 carbons;

21 R_6 through R_9 are independently selected from hydrogen, halogen,
22 alkyl of 1 to 10 carbons, halogen substituted alkyl of 1 to 10 carbons, alkoxy
23 of 1 to 10 carbons, halogen substituted alkoxy of 1 to 10 carbons,
24 alkylcarbonyl, alkoxycarbonyl the alkyl group in said alkylcarbonyl and
25 alkoxycarbonyl having 1 to 10 carbons, oxazolyl, imidazolyl, thiazolyl,
26 morpholinyl, piperazinyl, pyrazinyl, pyrazolyl, or any two adjacent ones of the
27 R_6 through R_9 groups may form a ring that may optionally include a

1 heteroatom selected from N, O and S and said ring may be further substituted;

2 R_{10} is hydrogen, alkyl of 1 to 10 carbons, or R_{10} may form an alkylene
3 chain together with R_3 ,

4 R_{11} and R_{12} are independently selected from hydrogen, halogen, alkyl
5 of 1 to 10 carbons and halogen substituted alkyl of 1 to 10 carbons;

6 R_{15} is selected from the formulas below

7

8

9

10

11

12

13

14

15

16

17 where

18 R_{16} is alkyl of 1 to 10 carbons, morpholino, piperidino, phenyl,

19 naphthyl or heteroaryl having 1 to 3 heteroatoms selected from N, O or S, said

20 morpholino, piperidino phenyl, naphthyl or heteroaryl groups being

21 unsubstituted, or substituted with 1 to 5 R_{17} groups;

22 R_{17} is alkyl of 1 to 10 carbons, halogen substituted alkyl of 1 to 10

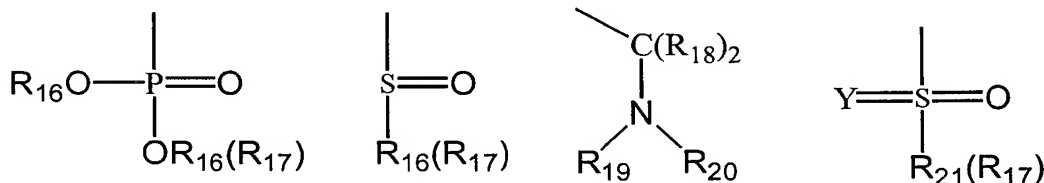
23 carbons, alkoxy having 1 to 10 carbons, halogen substituted alkoxy of 1 to 10

24 carbons, alkylthio having 1 to 10 carbons, halogen substituted alkylthio of 1 to

25 10 carbons, alkoxy carbonyl having 1 to 10 carbons, halogen substituted

26 alkoxy carbonyl having 1 to 10 carbons, F, Cl, Br, I, NO_2 , CN, OCOalkyl,

27 NH_2 , alkylamino and dialkylamino where in said OCOalkyl, , alkylamino and



1 dialkylamino groups each of said alkyl group has 1 to 10 carbons, further R_{17}
2 is ureidoyl (RNHCONH-), guanidinyl, carbamoyl, N-substituted carbamoyl,
3 alkylcarbonyl having 1 to 10 carbons, (alkoxycarbonyl)alkoxy groups of each
4 of said alkoxy group has 1 to 10 carbons, (alkoxycarbonyl)alkyl groups of
5 each of said alkoxy or alkyl group has 1 to 10 carbons, (carbamoyl)alkoxy
6 having 1 to 10 carbons, (N-alkylcarbamoyl)alkoxy having 1 to 10 carbons,
7 (N,N-dialkylcarbamoyl)alkoxy having 1 to 10 carbons, (N-substituted or
8 unsubstituted carbamoyl)poly(alkoxy) having 1 to 10 carbons, (N-substituted
9 or unsubstituted carbamoyl)alkyl having 1 to 10 carbons, [N-
10 (heteroaryl)carbamoyl]alkyl having 1 to 10 carbons, [N-
11 (heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted
12 heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted
13 aryl)carbamoyl]alkoxy having 1 to 10 carbons, poly(alkoxy) group of each of
14 said alkoxy group has 1 to 10 carbons, cyclic polyalkoxy (such as crown ether
15 moiety), guanidinyl group, ureido group, dialkylamino-poly(alkoxy) group,
16 [N-(carbamoylalkyl)carbamoyl]alkoxy, [N-(carbamoylalkyl)carbamoyl]alkyl,
17 [N-[[N-(heteroaryl) carbamoyl]alkyl]carbamoyl]alkoxy, [N-[[N-(substituted
18 heteroaryl) carbamoyl]alkyl]carbamoyl]alkoxy, [(tri-alkyl)ammonium]-
19 alkoxy, (sulfonato)alkyl, (sulfonato)alkoxy, N-[sulfonato)alkyl]amido,
20 (substituted)maleimido-, (substituted)succinimido;
21 R_{18} is independently selected from H, alkyl of 1 to 10 carbons and
22 phenyl;
23 R_{19} and R_{20} are independently selected from H, alkyl of 1 to 10
24 carbons, halogen substituted alkyl of 1 to 10 carbons, or R_{19} and R_{20} together
25 with the N atom may form a 4 to 10 membered ring that may include one more
26 heteroatom selected from N, O or S, said N heteroatom being unsubstituted or
27 substituted with an alkyl group of 1 to 10 carbons, or with an aryl or heteroaryl
28 group, and

1 R_{21} is alkyl, (aryl)alkyl, (heteroaryl)alkyl, phenyl, naphthyl or
2 heteroaryl having 1 to 3 heteroatoms independently selected from N, O and S,
3 said phenyl, naphthyl or heteroaryl groups being unsubstituted or substituted
4 with 1 to 5 R_{17} groups,

5 Y is O or $=NR_{16}$,

6 or to a pharmaceutically acceptable salt of said compounds.

7 The compounds of the invention are sulfoxides and have an asymmetric
8 center in the sulfur atom. Both the pure enantiomers, racemic mixtures and
9 unequal mixtures of the two are within the scope of the present invention.
10 Some of the compounds of the invention may have one or more asymmetric
11 carbon atoms (for example in a branch-chained alkyl group) and some other
12 compounds may have a second sulfoxide providing still another asymmetric
13 center in the sulfur atom. All optical isomers, racemates, diastereomers and
14 their mixtures are within the scope of the invention.

15 The compounds of the invention act as prodrugs of proton pump
16 inhibitor type drugs which are useful for inhibiting gastric acid secretion. The
17 compounds of the invention have excellent stability in tablet or capsule form,
18 are acid stable, have excellent bioavailability and plasma half life extending up
19 to 5 - 6 hours which is significantly longer than the plasma half life of the
20 presently used proton pump inhibitors.

21 DETAILED DESCRIPTION OF THE INVENTION

22 The chemical structure of the compounds of the invention is shown and
23 described in broad terms in the Summary of the Invention in connection with
24 **Formula 1**. As it can be seen in the formula, the compounds of the invention
25 are pyridyl methyl sulfinyl benzimidazoles, or compounds of closely related
26 structure, wherein one of the benzimidazole nitrogens is substituted with a
27 group (designated R_{15} in **Formula 1**) that gradually cleaves under
28 physiological conditions and thereby provides the pyridyl methyl sulfinyl

1 benzimidazole compound (or compound of closely related structure) which
2 has a free N-H function in the benzimidazole (or related) moiety. The
3 compound thus obtained by cleavage of the R_{15} group then undergoes the acid
4 catalyzed rearrangement and provides the thiophilic species which inhibits the
5 H,K-ATPase enzyme involved in gastric acid production. Thus, the novel
6 compounds of the present invention bearing the R_{15} group are prodrugs of the
7 proton pump inhibitor compounds which could also be depicted by **Formula**
8 **1**, where, however the R_{15} group would be designated hydrogen.

9 Generally speaking, among the prodrugs compounds of the present
10 invention those are preferred wherein the structure of the pyridyl methyl
11 sulfinyl benzimidazole or structurally related moiety is also preferred in the
12 prior art. In other words, preferably prodrugs are provided in accordance with
13 the present invention for those proton pump inhibitor drugs which are
14 themselves preferred.

15 Referring now to the specific designation of symbols in connection with
16 **Formula 1**, compounds are preferred in accordance with the present invention
17 wherein the moiety designated **Het₁** is pyridyl substituted with alkyl, O-alkyl
18 and/or O-fluoroalkyl groups. Most preferred substituents for the pyridine
19 moiety, designated R_1 , R_2 and R_3 in **Formula 1**, are CH_3O- , CH_3- , CF_3CH_2O-
20 and $CH_3O(CH_2)_3O-$.

21 The moiety designated **X** in **Formula 1** is preferably a methylene (-
22 CH_2 -) group, or a $-CHR_{10}$ group and the methylene or $-CHR_{10}$ group is
23 preferably attached in α position to the nitrogen in the pyridine moiety.
24 Compounds where the **X** is *ortho* phenylene or substituted *ortho* phenylene
25 are also preferred; in the most preferred compounds **X** is methylene.

26 Referring now to the group designated **Het₂** in **Formula 1**, this moiety
27 is preferably a substituted benzimidazole. The R_6 through R_9 groups
28 preferably are selected from hydrogen, chlorine and fluoro-substituted alkoxy

1 groups, with hydrogen, chlorine, $\text{CF}_2\text{HO-}$ and $\text{CH}_3\text{O-}$ being even more
2 preferred.

3 Referring now to the group designated \mathbf{R}_{15} in connection with
4 **Formula 1** it will be apparent to those skilled in the art that this group
5 represents the principal novel structural feature of the present invention.
6 Among the \mathbf{R}_{15} groups shown in connection with **Formula 1** the arylsulfonyl
7 groups (designated $\mathbf{R}_{21}(\mathbf{R}_{17})\text{SOY-}$ where Y is O) are preferred. In the
8 arylsulfonyl groups the aryl portion (\mathbf{R}_{21}) is preferably phenyl, substituted or
9 unsubstituted with the \mathbf{R}_{17} group. When the phenyl group (\mathbf{R}_{21}) is substituted,
10 then the substituent (\mathbf{R}_{17}) is preferably selected from Cl, Br, F, lower alkyl,
11 lower alkoxy, trifluoromethyl, trifluoromethoxy, di-(lower alkyl)amino, lower
12 alkoxycarbonyl, ureidoyl (RNHCONH-), guanidiny, carbamoyl, N-substituted
13 carbamoyl, (N-substituted carbamoyl)alkyl, di-(lower alkylamino)alkoxy,
14 (morpholin-4-yl)alkoxy, (morpholin-4-yl)polyalkoxy, di-(lower
15 alkylamino)alkyl, poly(alkoxy)alkoxy, cyclic poly(alkoxy),
16 (carbamoyl)alkoxy, [(N-(lower alkyl)carbamoyl]alkoxy, [N,N-(lower
17 dialkyl)carbamoyl]alkoxy, (N,N-dialkylcarbamoyl)alkyl, [N-
18 (heteroaryl)carbamoyl]alkyl, [N-(heteroaryl)carbamoyl]alkoxy, [N-
19 (aryl)carbamoyl]alkoxy, [N-[(N-substituted
20 carbamoyl)alkyl]carbamoyl]alkoxy, (sulfonato)alkyl, (sulfonato)alkoxy, N-
21 [sulfonato)alkyl]amido, (substituted)maleimido-, (substituted)succinimido and
22 [(tri-alkyl)ammonium]-alkoxy. Even more preferably the phenyl group is
23 unsubstituted (\mathbf{R}_{17} is H) or the substituent of the phenyl (\mathbf{R}_{21}) group is selected
24 from Cl, Br, F, methyl, methoxy, trifluoromethyl, trifluoromethoxy,
25 dimethylamino, ethoxycarbonyl, carbamoyl, guanidiny, ureidoyl,
26 (carbamoyl)methoxy, [N-(pyridyl)carbamoyl]methoxy, morpholinyl,
27 (morpholin-4-yl)alkoxy, [(morpholin-4-yl)alkoxy]alkoxy, 2-
28 (dimethylamino)ethoxy, [N-[(carbamoyl) methyl]carbamoyl]methoxy,

1 sodium(sulfonato)alkoxy, (trimethylammonium)alkoxy, poly(alkoxy), and
2 cyclic tetra- or penta-ethyleneoxy groups. Preferably there is only one R_{17}
3 substituent (other than hydrogen) in the phenyl (R_{21}) moiety, and preferably
4 the R_{17} substituent is in a position *para* (1,4) or *meta* (1,3) to the sulfonyl
5 (SO_2) group.

6 In other embodiments of the compounds of the invention the
7 physiologically labile substituent R_{15} is a sulfinyl group, designated
8 $R_{16}(R_{17})SO-$ in connection with **Formula 1**. Preferred groups for the $R_{16}(R_{17})$
9 combination are the same as for the $R_{21}(R_{17})$ combination, still more preferred
10 are phenyl, 4-methylphenyl, 4-methoxyphenyl and 4-trifluoromethylphenyl.
11 In this specification lower alkyl or lower alkoxy has 1 to 6 carbons.

12 In still other embodiments of the compounds of the invention the
13 physiologically labile substituent R_{15} forms a *Mannich* base, designated
14 $R_{19}R_{20}N-C(R_{18})_2-$ in connection with **Formula 1**. In these *Mannich* base type
15 compounds R_{18} is preferably H or lower alkyl, most preferably H or methyl.
16 The $R_{19}R_{20}N$ groups preferably are di-(lower alkyl)amino, *N*-succinimidyl, *N*-
17 morpholinyl, *N*-piperidinyl, *N*-(*N*-4-methyl)hexahydropyrazinyl, *N,N*-
18 phenyl,methyl-amino, *N*-tetrahydropyrrolyl, and *N*-(benzotriazol-1-yl), as
19 depicted below and designated respectively by formulas 2 through 8 and 8a:

20

21

22

23

24

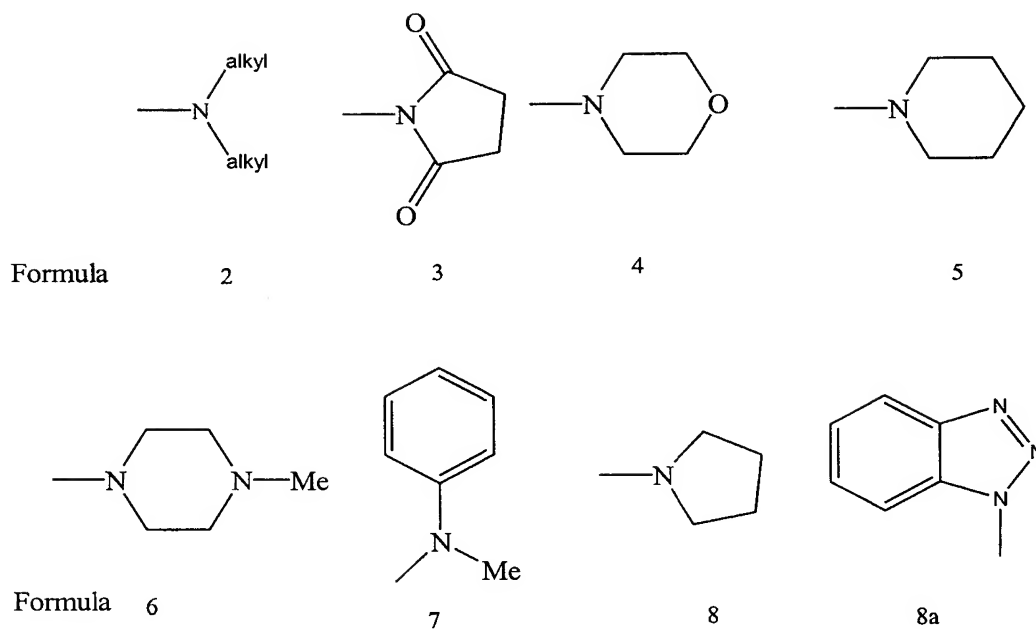
25

26

27

28

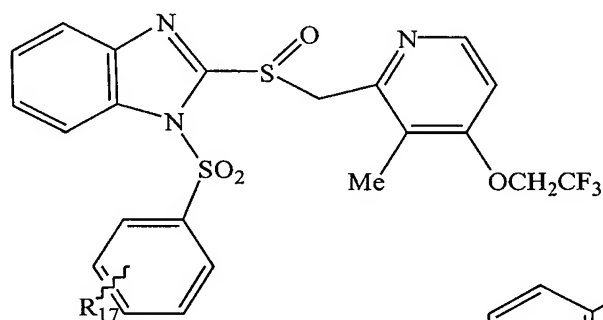
1
2
3
4
5
6
7
8
9
10
11
12



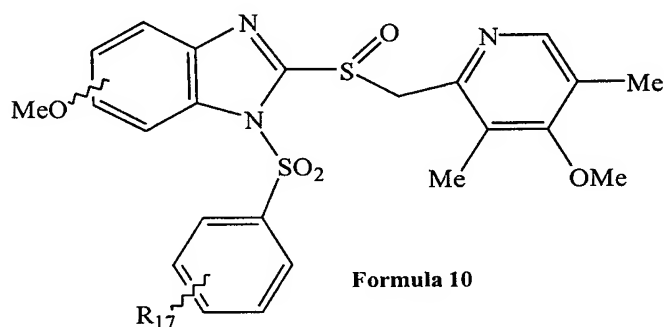
The most preferred groups for the $R_{19}R_{20}N$ - combination in accordance with the present invention are dimethylamino, *N*-morpholino, and *N*-piperidinyl.

The most preferred compounds of the invention are those wherein the proton pump inhibitor portion is the same as in the widely used proton pump inhibitor drugs known under the names LANSOPRAZOLE, OMEPRAZOLE, PANTOPRAZOLE and RABEPRAZOLE and wherein the R_{15} group is a benzenesulfonyl group mono-substituted either in the 4 (*para*) or in the 3 (*meta*) position with a Cl, Br, F, CH₃, CH₃O, CF₃, CF₃O-, (CH₃)₂N NH₂CO, NH₂CONH, NH₂C(=NH)NH, 4-morpholino, 2-(4-morpholinyl)ethoxy, 2-[2-(4-morpholinyl)ethoxy]ethoxy, 3-(4-morpholinyl)propoxy, poly(alkoxy), Na⁺ O₃S-CH₂CH₂CH₂-O, X⁻ (CH₃)₃N⁺CH₂CH₂O- (X is an anion, such as a halogen ion), NH₂COCH₂O, (pyridyl)NHCOCH₂O, NH₂COCH₂NH₂COCH₂O, (CH₃)₂NCH₂ or EtOCO group. These compounds are shown by **Formulas 9, 10, 11 and 12**, respectively, where R_{17}^* represents said Cl, Br, F, CH₃, CH₃O, CF₃, CF₃O-, (CH₃)₂N, NH₂CO, NH₂CONH, NH₂C(=NH)NH, 4-morpholino, 2-(4-morpholinyl)ethoxy, 2-[2-

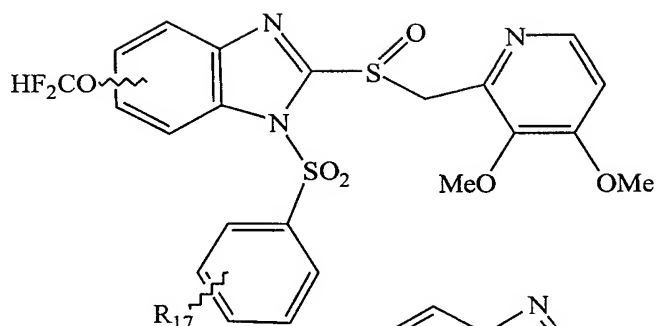
1 (4-morpholinyl)ethoxy]ethoxy, 3-(4-morpholinyl)propoxy, poly(alkoxy),
 2 $\text{NH}_2\text{COCH}_2\text{O}$, (pyridyl) NHCOCH_2O , $\text{NH}_2\text{COCH}_2\text{NH}_2\text{COCH}_2\text{O}$, $(\text{CH}_3)_2\text{NCH}_2$,
 3 $\text{Na}^+ \text{ } ^-\text{O}_3\text{S-CH}_2\text{CH}_2\text{CH}_2\text{-O}$, $(\text{CH}_3)_3\text{N}^+\text{CH}_2\text{CH}_2\text{O-}$, or EtOCO groups in the 4
 4 (*para*) or in the 3 (*meta*) position of the phenyl ring, and where the numbering
 5 of the benzimidazole ring is shown in the formulas. In **Formula 10** the
 6 $\text{CH}_3\text{O-}$ group can occupy the 5 or the 6 position of the benzimidazole moiety,
 7 and in **Formula 11** the $\text{CF}_2\text{HO-}$ group can occupy the 5 or the 6 position of the
 8 benzimidazole moiety.



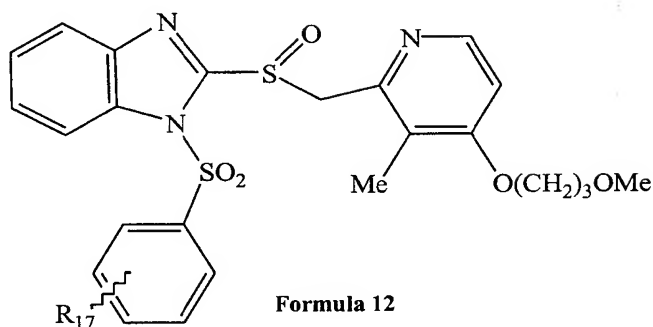
Formula 9



Formula 10



Formula 11



Formula 12

The compounds of the invention include

2-[[[(3-chloro-4-morpholino-2-pyridyl)methyl]sulfinyl]-5-methoxy-(1H)-benzimidazole,

2-[[[4-(2,2,3,3,4,4,4-heptafluorobutyl)oxy]-2-pyridyl]methyl]sulfinyl]-1H-thieno[3,4-d]imidazole,

2-[[[(4-ethylthio-3-methyl-2-pyridyl)methyl]sulfinyl]-1h-benzimidazole

2-[(3-methoxyphenyl)methylsulfinyl]-1H-benzimidazole,

2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[5,4-c]pyridine,

2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[4,5-c]pyridine,

and 2-[(3-methoxyphenyl)methylsulfinyl]-5-nitro-benzimidazole, of which 1-position have R_{15} group. R_{15} group of these compounds is a benzenesulfonyl

group mono-substituted either in the 4 (para) or in the 2 (meta) position with a

Cl, Br, F, CH_3 , CH_3O , CF_3 , CF_3O , $(CH_3)_2N$, NH_2CO , NH_2CONH ,

$NH_2C(=NH)NH$, 4-morpholino, 2-(4-morpholinyl)ethoxy, 2-[2-(4-

- 1 morpholinyl)ethoxy]ethoxy, 3-(4-morpholinyl)propoxy, $\text{NH}_2\text{COCH}_2\text{O}$,
2 (pyridyl) NHCOCH_2O , $\text{NH}_2\text{COCH}_2\text{NH}_2\text{COCH}_2\text{O}$, $(\text{CH}_3)_2\text{NCH}_2$,
3 $\text{Na}^+ \text{O}_3\text{S-CH}_2\text{CH}_2\text{CH}_2\text{-O}$, $(\text{CH}_3)_3\text{N}^+\text{CH}_2\text{CH}_2\text{O-}$, or EtOCO group.
4 Examples of the presently most preferred compounds of the invention are as
5 follows:
6 1-benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
7 pyridyl)methylsulfinyl]-1H-benzimidazole,
8 1-benzenesulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
9 pyridyl)methylsulfinyl]-1H-benzimidazole,
10 1-benzenesulfonyl-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
11 pyridyl)methylsulfinyl]-1H-benzimidazole,
12 1-benzenesulfonyl-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
13 pyridyl)methylsulfinyl]-1H-benzimidazole,
14 1-benzenesulfonyl-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
15 pyridyl)methylsulfinyl]-1H-benzimidazole,
16 1-(p-chlorobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
17 pyridyl)methylsulfinyl]-1H-benzimidazole,
18 1-(p-chlorobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
19 pyridyl)methylsulfinyl]-1H-benzimidazole,
20 1-(p-chlorobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
21 pyridyl)methylsulfinyl]-1H-benzimidazole,
22 1-(p-chlorobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
23 pyridyl)methylsulfinyl]-1H-benzimidazole,
24 1-(p-chlorobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
25 pyridyl)methylsulfinyl]-1H-benzimidazole,
26 1-(p-bromobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
27 pyridyl)methylsulfinyl]-1H-benzimidazole,
28 1-(p-bromobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

- 1 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 2 1-(p-bromobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 3 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 4 1-(p-bromobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 5 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 6 1-(p-bromobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 7 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 8 1-(p-fluorobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 9 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 10 1-(p-fluorobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 11 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 12 1-(p-fluorobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 13 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 14 1-(p-fluorobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 15 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 16 1-(p-fluorobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 17 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 18 1-(p-methylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 19 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 20 1-(p-methylbenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 21 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 22 1-(p-methylbenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 23 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 24 1-(p-methylbenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 25 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 26 1-(p-methylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 27 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 28 1-(p-methoxybenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

- 1 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 2 1-(p-methoxybenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 3 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 4 1-(p-methoxybenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 5 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 6 1-(p-methoxybenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 7 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 8 1-(p-methoxybenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 9 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 10 1-(3-trifluoromethylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-
- 11 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 12 1-(3-trifluoromethylbenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-
- 13 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 14 1-(3-trifluoromethylbenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-
- 15 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 16 1-(3-trifluoromethylbenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-
- 17 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 18 1-(3-trifluoromethylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-
- 19 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 20 1-(p-trifluoromethoxybenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-
- 21 methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 22 1-(p-trifluoromethoxybenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-
- 23 methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 24 1-(p-trifluoromethoxybenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-
- 25 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 26 1-(p-trifluoromethoxybenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-
- 27 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 28 1-(p-trifluoromethoxybenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-

- 1 trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 2 1-(p-dimethylaminobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-
- 3 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 4 1-(p-dimethylaminobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-
- 5 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 6 1-(p-dimethylaminobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-
- 7 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 8 1-(p-ethoxycarbonylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-
- 9 methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 10 1-(p-ethoxycarbonylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-
- 11 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 12 1-(pyridine-3-sulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 13 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 14 1-(pyridine-3-sulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 15 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 16 1-(pyridine-3-sulfonyl)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 17 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 18 1-(pyridine-3-sulfonyl)-5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
- 19 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 20 1-(pyridine-3-sulfonyl)-6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
- 21 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 22 1-[4-[(morpholin-4-yl)phenyl]sulfonyl]-5-methoxy-2-[(3,5-dimethyl-4-
- 23 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 24 1-[4-[(morpholin-4-yl)phenyl]sulfonyl]-6-methoxy-2-[(3,5-dimethyl-4-
- 25 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 26 N-[4-[[5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 27 pyridyl)methyl]sulfinyl]benzimidazol-1-yl]sulfonyl]phenyl]urea,
- 28 N-[4-[[6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

- 1 pyridyl)methyl]sulfinyl]benzimidazol-1-yl)sulfonyl]phenyl]urea,
2 N-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
3 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl} phenyl)urea,
4 N-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-
5 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl} phenyl)urea,
6 N-(4-{[2-({[(3,4-di(methoxy)-2-pyridyl)methyl]sulfinyl}-5-(difluoromethoxy)-
7 benzimidazol-1-yl)sulfonyl} phenyl)urea,
8 N-(4-{[2-({[(3,4-di(methoxy)-2-pyridyl)methyl]sulfinyl}-6-(difluoromethoxy)-
9 benzimidazol-1-yl)sulfonyl} phenyl)urea,
10 15-{[2-({[4-(3-methoxypropoxy-3-methyl-2-
11 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl}-
12 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,
13 15-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
14 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl}-
15 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,
16 15-[(5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-
17 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]-
18 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,
19 15-[(6-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-
20 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]-
21 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,
22 15-[(5-(difluoromethoxy)-2-{{(3,4-dimethoxy-2-
23 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]-
24 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,
25 15-[(6-(difluoromethoxy)-2-{{(3,4-dimethoxy-2-
26 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]-
27 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,
28 2-{4-[(5-methoxy-2-{{(3,5-dimethyl-4-methoxy-2-

1 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
2 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
3 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
4 pyridyl)acetamide,
5 N-(carbamoylmethyl)-2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
6 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
7 2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
8 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
9 2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
10 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
11 pyridyl)acetamide,
12 N-(carbamoylmethyl)-2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
13 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
14 2-(4-{2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
15 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl} phenoxy)acetamide,
16 2-(4-{2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
17 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl} phenoxy)-N-(2-
18 pyridyl)acetamide,
19 N-(carbamoylmethyl)-2-(4-{2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
20 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl} phenoxy)acetamide,
21 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-
22 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
23 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-
24 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
25 pyridyl)acetamide,
26 N-(carbamoylmethyl)-2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-
27 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
28 2-{4-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-

1 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
2 2-{4-[(6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
3 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
4 pyridyl)acetamide,
5 N-(carbamoylmethyl)-2-{4-[(6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
6 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
7 2-(4-{[2-([4-(3-methoxypropoxy)-3-methyl-2-
8 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenoxy)acetamide,
9 2-(4-{[2-([4-(3-methoxypropoxy)-3-methyl-2-
10 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenoxy)-N-(2-
11 pyridyl)acetamide,
12 N-(carbamoylmethyl)-2-(4-{[2-([4-(3-methoxypropoxy)-3-methyl-2-
13 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenoxy)acetamide,
14 1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-5-(difluoromethoxy)-2-
15 [[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
16 1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-6-(difluoromethoxy)-2-
17 [[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
18 1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-5-methoxy-2-[(3,5-
19 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
20 1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-6-methoxy-2-[(3,5-
21 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
22 1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-2-[(3-methyl-4-
23 methoxypropoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
24 1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-2-[(3-methyl-4-(2,2,2-
25 trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
26 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[[[(4-(3-methoxypropoxy)-
27 3-methyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
28 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-5-(difluoromethoxy)-2-[(3,4-

- 1 dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 2 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-5-methoxy-2-[[[(3,5-dimethyl-
- 3 4-methoxy-2-pyridyl)methyl]sulfinyl]]-1H-benzimidazole,
- 4 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-6-(difluoromethoxy)-2-[[[(3,4-
- 5 dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 6 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-6-methoxy-2-[[[(3,5-dimethyl-
- 7 4-methoxy-2-pyridyl)methyl]sulfinyl]]-1H-benzimidazole,
- 8 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[[[3-methyl-4-(2,2,2-
- 9 trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 10 1-[{(N,N-dimethylamino)methyl}benzene-4-sulfonyl]-5-methoxy-2-[[[(3,5-
- 11 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 12 1-[2-acetamido-4-methyl-5-thiazolylsulfonyl]-5-methoxy-2-[[[(3,5-dimethyl-4-
- 13 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 14 1-(thiophene-2-sulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 15 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 16 1-[{(N,N-dimethylamino)methyl}benzene-4-sulfonyl]-6-methoxy-2-[[[(3,5-
- 17 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 18 1-[2-acetamido-4-methyl-5-thiazolylsulfonyl]-6-methoxy-2-[[[(3,5-dimethyl-4-
- 19 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 20 1-(thiophene-2-sulfonyl)-6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 21 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 22 1-(thiophene-2-sulfonyl)-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-
- 23 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 24 1-(thiophene-2-sulfonyl)-5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-
- 25 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 26 1-(thiophene-2-sulfonyl)-6-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-
- 27 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 28 1-(thiophene-2-sulfonyl)-]-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-

- 1 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 2 1-(phenylmethylsulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 3 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 4 1-(n-propanesulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 5 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 6 1-(n-butanesulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 7 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 8 1-(isopropylsulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 9 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 10 1-[(N,N-dimethylamino)benzene-4-sulfonyl]-5-methoxy-2-[[[(3,5-dimethyl-4-
- 11 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 12 1-(phenylmethylsulfonyl)-6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 13 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 14 1-(n-propanesulfonyl)-6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 15 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 16 1-(n-butanesulfonyl)-6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 17 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 18 1-(isopropylsulfonyl)-6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 19 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 20 1-[(N,N-dimethylamino)benzene-4-sulfonyl]-6-methoxy-2-[[[(3,5-dimethyl-4-
- 21 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 22 1-(pyridine-3-sulfonyl)-2-[[[(3-methyl-4-methoxypropoxy-2-
- 23 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 24 1-[4-(morpholin-4-yl)phenylsulfonyl]-2-[[[(4-(3-methoxypropoxy)-3-methyl-
- 25 2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 26 1-benzenesulfonyl-2-[[[(3-chloro-4-morpholino-2-pyridyl)methyl]sulfinyl]-5-
- 27 methoxy-(1H)-benzimidazole,
- 28 1-benzenesulfonyl-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-

1 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
2 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]-1H-benzimidazole,
3 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[5,4-
4 c]pyridine,
5 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[4,5-
6 c]pyridine,
7 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]-5-nitro-
8 benzimidazole,
9 1-benzenesulfonyl-2-[{2-(dimethylamino)phenyl}methylsulfinyl]-1H-
10 benzimidazole,
11 1-benznesulfonyl-2-[[[4-(2,2,3,3,4,4,4-heptafluorobutyl)oxy]-2-
12 pyridyl)methyl]sulfinyl]-1H-thieno[3,4-d]imidazole,
13 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[(3-
14 methoxyphenyl)methylsulfinyl]imidazolo{5,4-c}pyridine,
15 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[{2-
16 (dimethylamino)phenyl}methylsulfinyl]-1H-benzimidazole,
17 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-5-methoxy-2-
18 [[[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
19 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-6-methoxy-2-
20 [[[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
21 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-[[[(4-(3-
22 methoxypropoxy)-3-methyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
23 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-5-
24 (difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-
25 benzimidazole,
26 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-6-
27 (difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-
28 benzimidazole,

1 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-[[[3-methyl-4-
2 (2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,
3 1-(benzotriazol-1-yl)methyl-5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-
4 pyridyl]methyl]sulfinyl]-1H-benzimidazole,
5 1-(benzotriazol-1-yl)methyl-6-methoxy-2-[[3,5-dimethyl-4-methoxy-2-
6 pyridyl]methyl]sulfinyl]-1H-benzimidazole,
7 1-(benzotriazol-1-yl)methyl-2-[[4-(3-methoxypropoxy)-3-methyl-2-
8 pyridyl]methyl]sulfinyl]-1H-benzimidazole,
9 diethyl [5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-
10 pyridyl]methyl]sulfinyl]benzimidazol-1-yl]phosphate,
11 1-(4-acetaminobenzenesulfonyl)-5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-
12 pyridyl]methyl]sulfinyl]-1H-benzimidazole,
13 1-(4-acetaminobenzenesulfonyl)-6-methoxy-2-[[3,5-dimethyl-4-methoxy-2-
14 pyridyl]methyl]sulfinyl]-1H-benzimidazole,

15 The compounds of the invention wherein the R_{15} group is an
16 arylsulfonyl group, can be prepared by the reacting the 2-
17 pyridylmethylsulfinyl-1H-benzimidazole derivatives (or structurally related
18 compounds) having a free NH group within the imidazole moiety, with an
19 arylsulfonyl chloride. In the broad sense the benzimidazole or structurally
20 related compound which is the starting material having the free NH group, can
21 be described by **Formula 1** wherein the R_{15} group would be H. Similarly, in
22 the broad sense the arylsulfonyl chloride reagent is described by the formula
23 $R_{21}(R_{17})SO_2Cl$ where the R_{21} and R_{17} groups are defined as in connection with
24 **Formula 1**. **Reaction Scheme 1** discloses a process for preparing exemplary
25 preferred compounds of the invention by reacting the 2-pyridylmethylsulfinyl-
26 1H-benzimidazole derivative of **Formula 13** with a benzenesulfonyl chloride
27 derivative of **Formula 14** in the presence of a suitable base. The reaction is
28 typically conducted in an inert organic solvent, such as dichloromethane in the

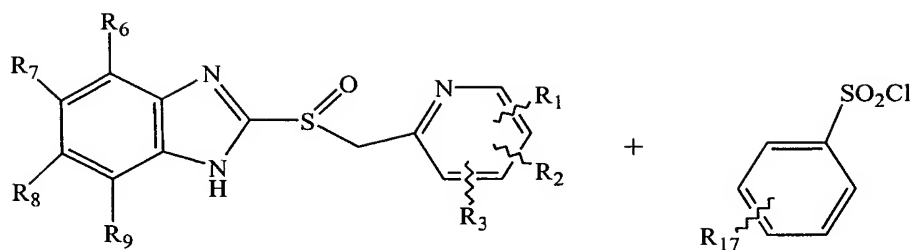
1 presence of an organic base, such as triethylamine. For compounds of
2 **Formula 13** and **Formula 14** the $R_1 - R_3$, $R_6 - R_9$ and R_{17} groups are defined
3 as in connection with **Formula 1**. As it can be seen in **Reaction Scheme 1**,
4 the benzenesulfonylation reaction may give rise to two isomeric or
5 tautomeric products depending on the nature and positions of the $R_6 - R_9$
6 substituents on the benzimidazole ring. The two isomeric products (which
7 may be merely taumers) are shown in **Formulas 15** and **16**.

8 The benzenesulfonyl chloride derivatives of **Formula 14** can be
9 obtained in accordance with procedures well known in the art.

10 Those skilled in the art will recognize the 2-pyridylmethylsulfinyl-1H-
11 benzimidazole derivatives of **Formula 13** as the proton pump inhibitors
12 generally known in the art and described for example in United States Patent
13 No. 4,686,230 (*Rainer et. al.*) and in published international application WO
14 97/48380 (*Astra Aktiobiolog*). Starting materials within the scope of **Formula**
15 **13** include the known drugs LANSOPRAZOLE (United States Patent No.
16 4,628,098), OMEPRAZOLE (United States Patent Nos. 4,255,431 and
17 4,255,431), PANTOPRAZOLE (United States Patent No. 4,758,579) and
18 RABEPRAZOLE (United States Patent No. 5,045,552) Thus, the starting
19 compounds of **Formula 13** can be prepared in accordance with the state-of-
20 the-art, for example as described in United States Patent Nos. 4,686,230,
21 4,628,098, 4,255,431, 4,758,579, 5,045,552, international application WO
22 97/48380, Journal of Medicinal Chemistry, 32, 1970-1977 (1989), Chem.
23 Pharm. Bull. 38, 2853-2858 (1990), J. Med. Chem., 34, 1049-1062 (1991),
24 Journal of Medicinal Chemistry, 35, 1049-1057 (1992), and Journal of
25 Medicinal Chemistry, 35, 438-450 (1992), all of which are specifically
26 incorporated herein by reference.

27 Although this is not shown in the reaction scheme, to obtain compounds
28 of the invention where with reference to **Formula 1** R_{15} is $R_{21}(C_6H_4)SO_2$ and

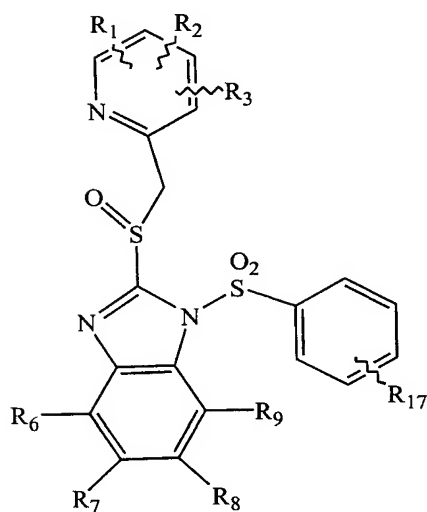
1 Y is $=NR_{16}$, a reagent of the formula $R_{21}(C_6H_4)S(O)(Cl)NR_{16}$ is used instead
2 of the reagent of **Formula 14**, to react with the compounds of **Formula 13**.
3 The reagent of the formula $R_{21}(C_6H_4)S(O)(Cl)NR_{16}$ can be obtained in
4 accordance with methods known in the art, for example as described in the
5 treatise COMPREHENSIVE ORGANIC FUNCTIONAL GROUP
6 TRANSFORMATIONS, Volume 7, Editors-in-Chief A. R. Katritzky, O.
7 Meth-Cohn and C. W. Rees (Pergamon).



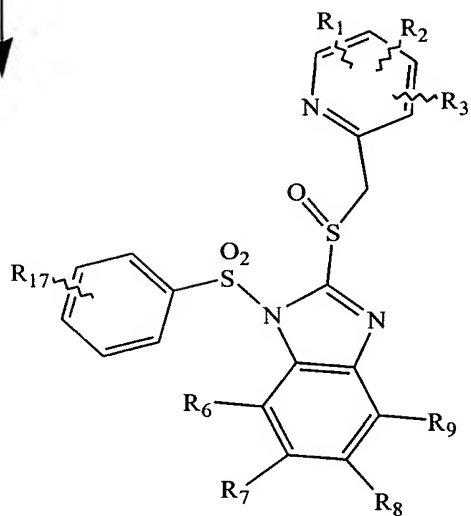
Formula 13

Formula 14

BASE



Formula 15

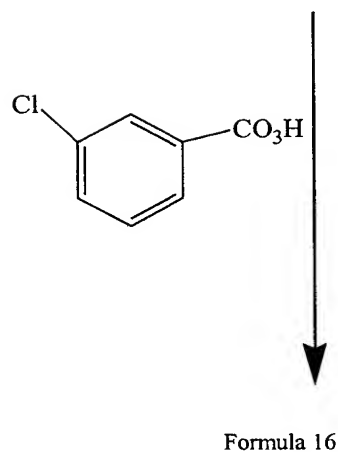
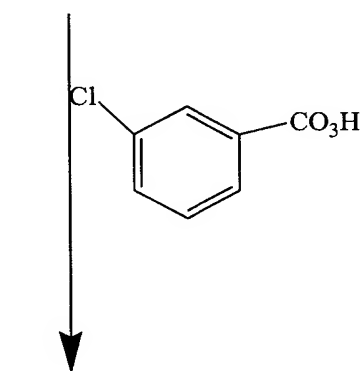
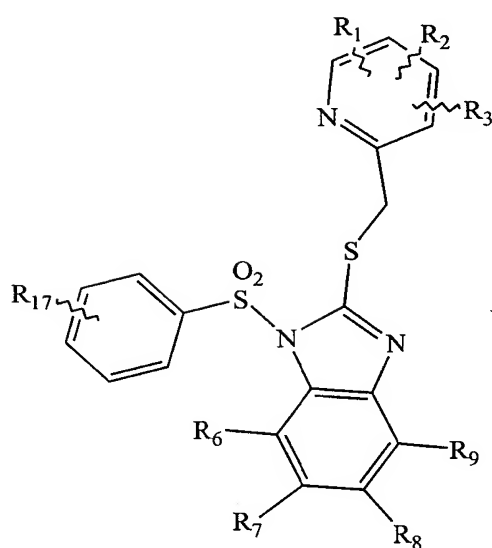
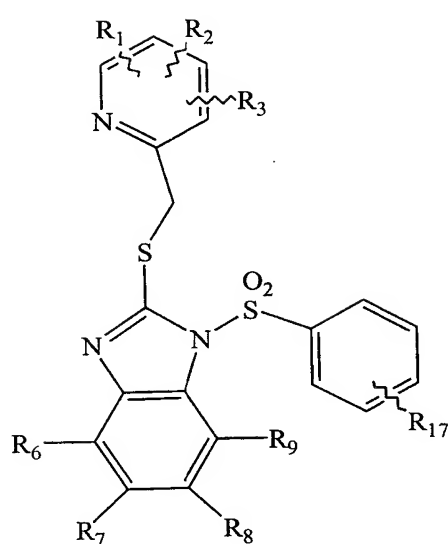


Formula 16

Reaction Scheme 1

1 Instead of using the free benzimidazole compounds of **Formula 13**,
2 their suitable salts such as the sodium, potassium, magnesium (and other) salts
3 can be reacted with the benzenesulfonyl chloride derivative of **Formula 13**, to
4 also provide the exemplary compounds of the invention in accordance with
5 **Formulas 15 and 16**.

6 **Reaction Scheme 2** discloses an alternative method for preparing the
7 exemplary compounds of the invention, shown in **Formulas 15 and 16**. This
8 reaction involves the oxidation of the corresponding 1-(*N*)-benzenesulfonyl-
9 benzimidazolyl, 2-pyridylmethyl sulfide compounds of **Formulas 17 and 18** to
10 the corresponding sulfoxides. Those skilled in the art will recognize that
11 **Formulas 17 and 18** represent isomeric compounds which may be different or
12 identical (tautomeric) with one another depending on the nature and position
13 of the **R₆ - R₉** substituents. The oxidation reaction can be performed with
14 oxidizing agents known in the art for forming sulfoxides, for example
15 hydrogen peroxide, *m*-chloroperoxybenzoic acid and iodosobenzene may serve
16 for this purpose. The oxidation reaction is normally conducted in an aprotic
17 neutral solvent, such as dichloromethane. The sulfide compounds of
18 **Formulas 17 and 18** can be obtained by performing a benzenesulphonylation
19 reaction (in analogy to the reaction of **Scheme 1**) on the sulfide compounds
20 having a free benzimidazole NH group, or their suitable salt. The latter
21 sulfides (**Formulas 17 and 18**) can be obtained in accordance with the state-
22 of-the-art.



Reaction Scheme 2

1 The compounds of the invention where the physiologically labile R_{15}
2 group is $R_{16}(R_{17})SO$ (sulfinyl), as defined in connection with **Formula 1**, can
3 be made in reactions which are analogous to the reactions shown in **Scheme 1**,
4 except that instead of an arylsulfonyl chloride an arylsulfinyl chloride of
5 formula $R_{16}(R_{17})SOCl$ is used. The arylsulfinylation reaction is usually
6 conducted in the presence of an organic base, in a solvent such as dioxane,
7 tetrahydrofuran, or an alcohol. The arylsulfinyl chloride of formula
8 $R_{16}(R_{17})SOCl$ can be made from the corresponding sulfinic acid or salt having
9 the formula $R_{16}(R_{17})SO_2Na$, by treatment with thionyl chloride. In view of
10 their close analogy to the sulfonylation reactions of **Scheme 1**, the
11 sulfinylation reactions are not shown in a scheme.

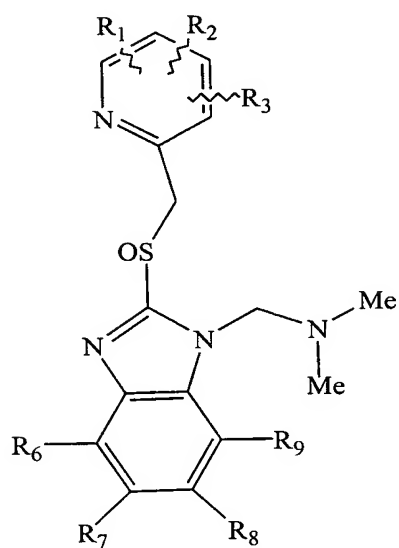
12 The compounds of the invention where the physiologically labile R_{15}
13 group together with the 2-pyridylmethylsulfinyl-1H-benzimidazole derivatives
14 (or structurally related compounds) form a *Mannich* base, can be made under
15 conditions which are generally applicable and known in the art for forming
16 *Mannich* bases. A specific detailed description for forming *Mannich* base
17 type prodrugs is provided by *Bundgaard et al.* in **Methods in Enzymology**
18 **112**, p347 -359 which is incorporated herein by reference. Generally
19 speaking, the preparation of *Mannich* base type prodrugs of this invention
20 involves heating a mixture of an amine of the formula $R_{19}R_{20}NH$ with an
21 aldehyde or ketone of the formula $OC(R_{18})_2$ in an alcohol, water, dioxane or
22 other suitable solvent. The symbols $R_{18} - R_{20}$ are defined as in connection
23 with **Formula 1**.

24 **Reaction Scheme 3** illustrates the preparation of exemplary *Mannich*
25 base type compounds of the invention from the 2-pyridylmethylsulfinyl-1H-
26 benzimidazole derivatives of **Formula 13** using formaldehyde as the aldehyde
27 and dimethylamine as the amine. As it can be seen in the reaction scheme, this
28 reaction also may provide two isomeric products of **Formula 19** and **20**,

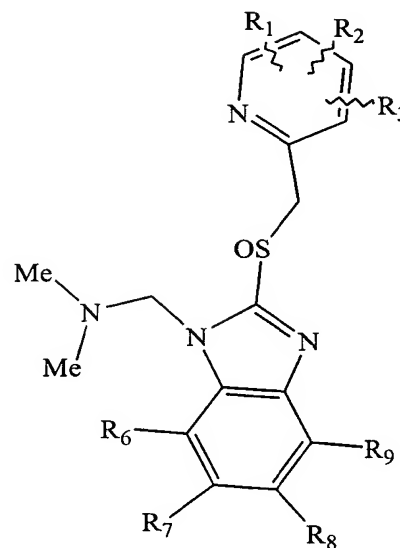
1 respectively. The two products may be identical (tautomeric) depending on
2 the nature and position of the R_6 - R_9 substituents.

Formula 13

CH_2O ,
 $\text{HN}(\text{Me})_2$,
 MeOH , heat



Formula 19



Formula 20

Reaction Scheme 3

1 The compounds of **Formula 19** and **Formula 20** can be and preferably
2 are prepared by an alternative method including a reaction of N-halomethyl
3 dialkylamines with a sodium salt of **Formula 13**, or a tetraammonium salt of
4 **Formula 13**, or with a compound of **Formula 13** in the presence of sodium
5 tert-butoxide. N-chloromethyl dialkylamines were prepared as described by
6 *Boehme et al.*, (Chemische Berichte, vol., 93, pp1305-1309 (1960) and
7 Chemische Berichte, vol., 95, pp 1849-1858(1962)), and a
8 tetra(alkyl)ammonium salt of **Formula 13** was prepared by a method
9 described in United States Patent No. 5,021,433. For example,
10 tetrabutylammonium salt of 2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]
11 sulfinyl]-5-methoxy-1H-benzimidazole was prepared as described in the
12 United States Patent No. 5,021,433 and used *in situ*. Tetrabutylammonium salt
13 of 2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-5-methoxy-1H-
14 benzimidazole was reacted with 1-chloromethyl-N,N-dimethylamine in
15 dichloromethane to give a mixture of 1-(N,N-dimethylamino)methyl-2-[[[(3,5-
16 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-5-methoxy-1H-benzimidazole
17 and 1-(N,N-dimethylamino)methyl-2-[[[(3,5-dimethyl-4-methoxy-2-
18 pyridyl)methyl]sulfinyl]-6-methoxy-1H-benzimidazole. 1-(Heteroaryl-N-
19 methyl)-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-(5 and 6-
20 methoxy)-1H-benzimidazole was synthesized by a similar method. For
21 example, a mixture of 1-(benzotriazol-1-yl)methyl-2-[[[(3,5-dimethyl-4-
22 methoxy-2-pyridyl)methyl]sulfinyl]-5-methoxy-1H-benzimidazole and 1-
23 (benzotriazol-1-yl)methyl-2-[[[(3,5-dimethyl-4-methoxy-2-
24 pyridyl)methyl]sulfinyl]-6-methoxy-1H-benzimidazole was prepared by a
25 reaction of sodium salt of 2-[[[(3,5-dimethyl-4-methoxy-2-
26 pyridyl)methyl]sulfinyl]-5-methoxy-1H-benzimidazole with 1-chloromethyl-
27 1H-benzotriazole.

28 Another method for preparing the compounds of **Formula 19** and

1 **Formula 20** is using a reaction of 1-chloromethyl-2-[(2-
2 pyridyl)methylsulfinyl]-1H-benzimidazole compounds with dialkylamines
3 such as morpholine, dimethylamine, pyrrolidine, and piperidine. 1-
4 Chloromethyl-2-[(2-pyridyl)methylsulfinyl]-1H-benzimidazole compounds
5 were prepared by a method described in European Pat., No. 279,149 (*Alminger*
6 *et al.*). For example, a mixture of 1-chloromethyl-5-methoxy-2-[[4-methoxy-
7 3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-
8 chloromethyl-6-methoxy-2-[[4-methoxy-3,5-dimethyl-2-
9 pyridyl)methyl]sulfinyl]-1H-benzimidazole was reacted with morpholine to
10 give a mixture of 1-(morpholin-4-yl)methyl-5-methoxy-2-[[4-methoxy-3,5-
11 dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(morpholin-4-
12 yl)methyl-6-methoxy-2-[[4-methoxy-3,5-dimethyl-2-
13 pyridyl)methyl]sulfinyl]-1H-benzimidazole.

14 A significant advantage of the compounds of the present invention is
15 that they can release the active forms of the proton pump inhibitors
16 spontaneously by hydrolysis in the mammalian (including human) body.
17 Hydrolysis can occur chemically or enzymatically. Because the compounds of
18 this invention spontaneously release the active form of the proton pump
19 inhibitor drugs by *in vivo* hydrolysis, they can attain longer duration of
20 effective drug concentration in the body. Thus, the compounds of the present
21 invention are prodrugs which are converted to active drugs by hydrolysis in
22 the body, providing long duration of effective concentration. The long duration
23 of inhibitory activity by spontaneous hydrolysis of the compounds of this
24 invention allows more effective inhibition of gastric acid secretion, which
25 enables better therapy of acid related disease as defined on p.1. and p.2.
26 Compounds of this invention can be administered for inhibiting gastric acid
27 secretion orally. The typical daily dose of the compounds will depend on
28 various factors such as the individual requirement of each patient. In general,

1 oral and parenteral dosages will be in the range of 5 to 100 mg per day.

2 Those skilled in the art will readily understand that for oral
3 administration the compounds of the invention are admixed with
4 pharmaceutically acceptable excipients which *per se* are well known in the art.
5 Specifically, a drug to be administered systemically, it may be confectioned as a
6 powder, pill, tablet or the like or as a syrup or elixir suitable for oral
7 administration. Description of the substances normally used to prepare tablets,
8 powders, pills, syrups and elixirs can be found in several books and treatise
9 well known in the art, for example in Remington's Pharmaceutical Science,
10 Edition 17, Mack Publishing Company, Easton, Pennsylvania.

11 Compounds of the present invention can be combined with certain
12 amounts of known proton pump inhibitors, *e. g.* LANSOPRAZOLE,
13 OMEPRAZOLE, PANTOPRAZOLE, or RABEPRAZOLE, to provide a
14 drug-prodrug combination, and the combination administered for inhibition of
15 gastric acid secretion. Thus, initially the proton pump inhibitor (drug) inhibits
16 gastric acid secretion of the patient. The aforesaid known and widely used
17 proton pump inhibitors have 60-90 minutes of plasma half-life. As the
18 effective concentration of the proton pump inhibitor (drug) is decreased by
19 metabolism, the compounds of the present invention (prodrug) continuously
20 undergoes hydrolysis and provides and maintains new active inhibitor
21 concentration in the mammalian, including human body.

22 A disadvantage of the presently used proton pump inhibitors is that for
23 therapy by injection in a liquid form they must be reconstituted from a
24 lyophilized powder in a medium having the high pH of approximately 9.5.
25 The prodrugs of the present invention overcome the disadvantage of requiring
26 a reconstituting medium having such high pH, because the compounds of the
27 present invention can be reconstituted to form an injectable liquid in a medium
28 of approximately pH 6.0 to 8.5. It will be readily appreciated by those skilled

1 in the art that for administration in liquid form by injection the liquid that
2 reconstitutes the drug is a pharmaceutically acceptable aqueous solution that
3 *per se* is known in the art. Such pharmaceutically acceptable solutions utilized
4 for administration of drugs in injectable form are described for example in the
5 treatise PHARMACEUTICAL DOSAGE FORMS (Parenteral Medications,
6 Volume 1, Edited by K. E. Avis, H. A. Lieberman and L. Lachman (1992).

7 Among the benefits of the pre-proton pump inhibitor (P-PPI) type of
8 drugs of the present invention is their ability to provide more effective
9 treatment of erosive esophagitis and of less severe reflux diseases as well.
10 This is because effective treatment of erosive esophagitis (and to a lesser
11 extent of lesser reflux diseases) requires prevention of the reflux of gastric
12 contents at pH 3.0 or still lower pH. The current PPI drugs allow several
13 acidic excursions to pH < 2.0 per day, resulting in a moderate to weak
14 amelioration of symptoms. However, healing would require elevation to pH
15 > 4.0 for about 16 hours per day or longer. When, as in current usual
16 treatment by PPIs, the other 8 hours contain episodic acidity to pH 3.0 or less,
17 the patients tend to continue to complain of pain. The more effective and
18 more continues acid suppression by the drugs of the present invention is likely
19 to result in substantially better treatment of this disease, as well as faster
20 healing of all acid related erosions or ulcers.

21 The pre-proton pump inhibitor (P-PPI) type of drugs of the present
22 invention provide improved dual therapy for *H. pylori* eradication. This is
23 because the PPI's synergize with cell division dependent antibiotics such as
24 amoxicillin (cell wall biosynthesis) and clarithromycin (protein synthesis) by
25 elevating gastric surface pH to enable a larger fraction of the bacterial
26 population to be in dividing phase during presentation of the antibiotic to the
27 gastric lumen. However, their effect on intragastric pH is limited by their
28 dwell time in the plasma. The pre-proton pump inhibitor (P-PPI) type of drugs

1 of the present invention can continuously elevate intragastric pH close to
2 neutrality on current once a day therapy. Therefore, 100% eradication of the
3 bacteria is expected in dual therapy with the prodrugs of the invention (for
4 example a pro-drug of OMEPRAZOLE in accordance with the invention) plus
5 an effective antibiotic, such as amoxicillin.

6 Even monotherapy for *H. pylori* eradication is likely to be successful
7 with the pre-proton pump inhibitor (P-PPI) type of drugs of the present
8 invention. This is because in the absence of acid, the enzyme *H. pylori* urease
9 elevates environmental pH to > 8.3 , which is toxic to the organism. PPI's in
10 current formulation inhibit growth or present of the organism in the antrum,
11 due to elevation of antral pH to close to neutrality. Elevation of 24 hour pH to
12 neutrality, as it can be accomplished with the drugs of the present invention, is
13 likely to result in "self eradication" of the bacteria.

14 Approximately 30% of patients with gastrointestinal distress appear
15 with symptoms without quantitative underlying disease (non-ulcer dyspepsia).
16 The most likely cause for these symptoms is upper gastrointestinal afferent
17 nerve sensitivity to gastric acid. Only acid ablation ameliorates these
18 symptoms and this can be attained with the drugs of the present invention.

19 By way of concrete examples, the following tests and results are
20 described. Certain compounds of the invention have been tested in one or
21 more standard laboratory tests that demonstrate gastric antiseecretory activity.
22 The compounds of the invention did not directly inhibit the K^+ -dependent
23 ATP hydrolysis of gastric H,K-ATPase. However, after hydrolysis the
24 compounds of this invention showed strong inhibition of gastric H,K-ATPase
25 activity. This is consistent with the knowledge that the compounds obtained
26 by hydrolysis *e. g.* LANSOPRAZOLE, OMEPRAZOLE, PANTOPRAZOLE
27 and RABEPRAZOLE are well known H,K-ATPase inhibitors. For example,
28 1-benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

1 pyridyl)methylsulfinyl]-1H-benzimidazole was tested for inhibitory activity of
2 gastric H,K-ATPase. Initially this compound did not inhibit gastric H,K-
3 ATPase. However, gastric H,K-ATPase activity was spontaneously inhibited
4 as hydrolysis of this compound in aqueous solution at pH 7.4 proceeded. After
5 5.75 hr -hydrolysis at pH 7.4, this compound inhibited 91% of gastric H,K-
6 ATPase activity, same as 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
7 pyridyl)methylsulfinyl]-1H-benzimidazole (OMEPRAZOLE) which was the
8 product of the hydrolysis. It was determined that 1-benzenesulfonyl-5-
9 methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-
10 benzimidazole was hydrolyzed to 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
11 pyridyl)methylsulfinyl]-1H-benzimidazole (OMEPRAZOLE) with a half-life
12 ($t_{1/2}$) 3 ± 0.5 hr at 37 °C at pH 7.4.

13 When a mixture of 2-{4-[(5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
14 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
15 pyridyl)acetamide and 2-{4-[(6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
16 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
17 pyridyl)acetamide was orally administrated to male rat, 5-methoxy-2-[(3,5-
18 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole
19 (OMEPRAZOLE) was continuously released to the plasma for more than 4
20 hours as a result of the hydrolysis of 2-{4-[(5-methoxy-2-[(3,5-dimethyl-4-
21 methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-
22 (2-pyridyl)acetamide and 2-{4-[(6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
23 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
24 pyridyl)acetamide. As a control experiment, when OMEPRAZOLE was
25 administrated to male rat, OMEPRAZOLE Has completely disappeared from
26 the plasma within 1.5 hr. Bioavailability of 2-{4-[(5-methoxy-2-[(3,5-
27 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-
28 yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide was much higher than that of

1 OMEPRAZOLE after oral administration.

2 When a mixture of 2-{4-[(5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
3 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
4 pyridyl)acetamide and 2-{4-[(6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
5 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
6 pyridyl)acetamide was orally administered to male rat, gastric acid secretion
7 was significantly and continuously inhibited. After 5 hours of oral
8 administration, a mixture of 2-{4-[(5-methoxy-2-[(3,5-dimethyl-4-methoxy-
9 2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
10 pyridyl)acetamide and 2-{4-[(6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
11 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
12 pyridyl)acetamide provided maximum 90% of inhibition of gastric acid
13 secretion stimulated by histamine, while OMEPRAZOLE provided only about
14 45% of inhibition. There is a report that 50-60% of inhibition of gastric acid
15 output is obtained after 4 to 6 hours of intravenous administration of
16 OMEPRAZOLE (*Katashima, et al.*, Drug metabolism and Disposition, vol.,
17 23, 718-723, 1995). Probably, lower inhibition (45 %) of gastric acid
18 production after administration of OMEPRAZOLE in this experiment,
19 compared to the reported data (50-60 %) obtained by Katashima. et al, is due
20 to the different method of administration. However, it is well known that oral
21 potency of OMEPRAZOLE without enteric-coating is significantly lower than
22 that found after i.v. or i.d. administration in both rat and dog (*Larsson et al.*,
23 Scand. J. Gastroenterology, vol. 20 (suppl. 108), 23-35, 1985). The
24 compounds of this invention do not need enteric-coating for protection from
25 acid-catalyzed decomposition. Furthermore, the compounds of this invention
26 provide continuous inhibition of gastric acid secretion. Maximum inhibition
27 by the compound of 2-{4-[(5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
28 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-

1 pyridyl)acetamide and 2- {4-[(6-methoxy-2- {[(3,5-dimethyl-4-methoxy-2-
2 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
3 pyridyl)acetamide obtained after 5 hours shows that the compounds of the
4 invention are continuously converted to the corresponding PPI in vivo, which
5 inhibits gastric acid secretion.

6 SPECIFIC EMBODIMENTS AND EXPERIMENTAL 7 DESCRIPTION

8 Preparation of Intermediates

9 Reference Example 1: Preparation of [(morpholin-4-yl)alkoxy]benzene-4-
10 sulfonyl chloride

11 [(morpholin-4-yl) alkoxy] benzene-4-sulfonyl chloride was prepared by
12 chlorosulfonylation of 4-[(phenoxy)alkoxy]morpholine using chlorosulfonic
13 acid in the presence of dichloromethane or chloroform. In this reaction,
14 chloroform or dichloromethane was important to avoid the cleavage of ether
15 linkage of alkoxybenzene moiety by chlorosulfonic acid.

16 [3-(Morpholin-4-yl) propoxy] benzene-4-sulfonyl chloride was prepared by
17 chlorosulfonylation of 4-(3-phenoxypropyl)morpholine using chlorosulfonic
18 acid in the presence of dichloromethane or chloroform. For example, to a
19 solution of 2.2 g (10 mmole) of N-(3-phenoxypropyl) morpholine in 20 ml of
20 chloroform, 2 ml of chlorosulfonic acid (30 mmole) was slowly added at -10
21 °C and stirred for 30 min. The reaction mixture was stirred at room
22 temperature for 5 hr. Chloroform was removed from lower layer. Lower layer
23 was treated with chopped-ice to give solids. To a mixture of ice and solid
24 product, 10 g of sodium phosphate (tribasic) was added and stirred with
25 cooling. Chlorosulfonyl compound was extracted with dichloromethane (300
26 ml). Dichloromethane extract was dried over anhydrous magnesium sulfate
27 and evaporated under reduced pressure. 1.6 g of [3-(morpholin-4-yl) propoxy]
28 benzene-4-sulfonyl chloride was obtained.

1 [2-(Morpholin-4-yl)ethoxy]benzene-4-sulfonyl chloride was prepared using N-
2 (2-phenoxyethyl) morpholine by similar reaction described above. For
3 example, 7.2 g of N-(2-phenoxyethyl)morpholine HCl salt was resuspended in
4 20 ml of dichloromethane and 7 ml of chlorosulfonic acid was slowly
5 introduced with cooling by ice-jacket. The reaction mixture was stirred at 0 °C
6 for 2 hr, then, at room temperature overnight. Dichloromethane (350 ml) was
7 added to the reaction mixture and excess chlorosulfonic acid was destroyed by
8 adding icy water(about 100 g). Aqueous layer was adjusted to pH 8.5 by
9 concentrated sodium carbonate solution with cooling by ice. Dichloromethane
10 was dried over anhydrous magnesium sulfate and evaporated under reduced
11 pressure to give 8.1 g of [2-(morpholin-4-yl)ethoxy]benzene-4-sulfonyl
12 chloride. M.P. 48-50 °C.

13 N-(2-Phenoxyethyl) morpholine was prepared by a modified method of Grail.
14 et al (Journal of American Chemical Society, 1952, 74, 1313-1315). For
15 example, 9.2 g of phenol and 18.6 g of N-(2-chloroethyl)morpholine HCl salt
16 were dissolved in 120 ml of isopropanol and 12 g of potassium hydroxide was
17 added with cooling. The reaction mixture was refluxed for 12 hours. Solid
18 (KCl) was filtered off. The filtrate was distilled off. The residual material was
19 treated with 150 ml of 1 N NaOH, then, extracted with dichloromethane (200
20 ml). Dichloromethane layer was again washed with a solution of 0.1 N sodium
21 carbonate in 10% NaCl solution. Dichloromethane layer was dried over
22 anhydrous magnesium chloride, and evaporated under reduced pressure.
23 Residual syrup was dissolved in 100 ml of 1.5 N HCl solution, and washed
24 with 100 ml of chloroform. Aqueous layer was treated with 100 ml of toluene
25 and water was removed by Dean-Stark apparatus by distillation. Residual
26 toluene layer was cooled to give crystalline solid, which was collected by
27 filtration. 12 g of N-[(2-phenoxy)ethyl]morpholine HCl salt (50% yield)was
28 obtained.

1 N-[3-(Phenoxy)propyl] morpholine was prepared by a reaction of 3-
2 (phenoxy)propyl bromide with morpholine. For example, 3-(phenoxy)propyl
3 bromide (7.8 ml, 50 mmole) was added to morpholine (8 ml) in toluene (50
4 ml) and refluxed overnight. NaOH solution (2 g of NaOH in 20 ml of water)
5 was added and additionally refluxed for 4 hr. Toluene was removed by
6 distillation under reduced pressure. Residue was treated with
7 dichloromethane(200 ml) and water(200 ml). Dichloromethane layer was dried
8 and concentrated. Residue was treated with dichloromethane-heptane to give 7
9 g of 4-[3-(phenoxy)propyl] morpholine.

10 [2-{2-(Morpholin-4-yl)ethoxy}ethoxy]benzene-4-sulfonyl chloride was
11 prepared using 4-[2-[2-(phenoxy)ethoxy]ethyl]morpholine by a similar
12 reaction described above. For example, 2-(phenoxy)ethanol (4.0 ml) was
13 added to 5.4 g of N-(2-chloroethyl)morpholine hydrochloride and 6 g of
14 sodium tert-butoxide in 70 ml of toluene. The reaction mixture was refluxed
15 for 16 hr. EtOAc (100 ml) was added and washed with water (200 ml).
16 Organic layer was separated, and again, extracted with 0.5 N HCl solution
17 (120 ml). Aqueous layer was washed again with chloroform (30 ml), then, was
18 adjusted to pH 10.5 by adding NaOH solution. The product, [2-[2-(morpholin-
19 4-yl)ethoxy]ethoxy]benzene, was extracted with dichloromethane (200 ml)
20 from water. Organic layer was again washed with water, dried over anhydrous
21 magnesium sulfate, and concentrated under reduced pressure. The product, [2-
22 [2-(morpholin-4-yl)ethoxy]ethoxy]benzene, was obtained as a yellow syrup
23 (5.4 g). TLC analysis showed over 99% purity and the structure was confirmed
24 by NMR. The syrupy product was used in situ for preparing [2-{2-(morpholin-
25 4-yl)ethoxy}ethoxy]benzene-4-sulfonyl chloride.

26 5.0 g of 2-[2-(morpholin-4-yl)ethoxy]ethoxybenzene was dissolved in 70 ml
27 of dichloromethane. In ice bath, chlorosulfonic acid (7 ml) was slowly added.
28 The reaction mixture was stirred at room temperature overnight. Two layers

1 were separated. Chloroform layer, upper layer, was removed. Pale brown
2 syrup, lower layer, was added to 100 g of chopped ice. Dichloromethane (200
3 ml) was added, and concentrated sodium carbonate solution was slowly added
4 upto pH 9 under 4 °C with good stirring. Dichloromethane layer was
5 separated, dried over anhydrous magnesium sulfate, and evaporated under
6 reduced pressure. Yellow syrup was obtained, which was dried in vacuo. 3.8 g
7 of [2-{2-(morpholin-4-yl)ethoxy}ethoxy]benzene-4-sulfonyl chloride was
8 obtained.

9 Reference Example 2: Preparation of [2-(dimethylamino)ethoxy]phenyl-4-
10 sulfonyl chloride

11 2 g of N,N-dimethyl-N-[(2-phenoxy)ethyl]amine was dissolved in 10 ml of
12 dichloromethane and 3 ml of chlorosulfonic acid was slowly added under ice
13 cooling. The mixture was stirred at room temperature for 3 hr and poured into
14 ice. Dichloromethane (100 ml) was added and aqueous layer was neutralized
15 by concentrated sodium carbonate solution with keeping temperature under 4
16 °C. Dichloromethane layer was dried over anhydrous magnesium sulfate and
17 evaporated under reduced pressure. 0.8 g of [2-
18 (dimethylamino)ethoxy]phenyl-4-sulfonyl chloride was obtained.

19 Reference Example 3: Preparation of N-[4-(chlorosulfonyl)phenyl]urea

20 N-[4-(chlorosulfonyl)phenyl]urea was prepared by a known method (R. J. W.
21 Cremlyn, D. Leonard, and R. Motwani (1973) J. Chem. Soc., Perkin I 500-
22 503).

23 Chlorosulfonic acid (4.4 ml) was added to phenylurea (2.7 g) in an ice bath,
24 then, warmed to 60 °C for 3 hr. The syrup was poured on chopped ice with
25 good mixing. Solid was separated and dried in vacuo. 2.3 g of product was
26 obtained. M.P. 138-141 °C.

27 Reference Example 4: Preparation of N-[(p-chlorosulfonyl)phenyl]morpholine

28 N-[(p-Chlorosulfonyl)phenyl] morpholine was synthesized by a modified

1 method of Cremlyn, et al. (R. J. Cremlyn, J. P. Bassin, S. Farouk, M.
2 Potterton, and T. Mattu. (1992) Phosphorus, Sulfur, and Silicon, Vol., 73, pp.
3 107-120).
4 10 g of 4-phenyl morpholine in 50 ml of chloroform was added to 25 ml of
5 chlorosulfonic acid in a ice-jacket. The reaction mixture was stirred at reflux
6 for 7 hr. Brown syrup was poured into dichloromethane (150 ml) and chopped
7 ice (100 g) with stirring, and neutralized by saturated sodium phosphate,
8 tribasic, with ice-cooling. Collect dichloromethane layer, dried over anhydrous
9 magnesium sulfate. Organic solvent was evaporated under reduced pressure to
10 give yellow solid, which was dried in vacuo. 6.1 g of product was obtained. M.
11 P. 154-156 °C.

12 Reference Example 5: Preparation of pyridine-3-sulfonyl chloride

13 Pyridine-3-sulfonyl chloride was prepared by a method of Alo, et al. (B. I.
14 Alo, O. B. Familoni, F. Marsais, and G. Queguiner, (1992) Journal of
15 Heterocyclic Chemistry, vol. 29, pp 61-64.)
16 24 g of phosphorus pentachloride was added to a suspension of 15 g of
17 pyridine-3-sulfonic acid in 30 ml of phosphorus oxychloride and heated at 120
18 °C for 12 hr. The reaction mixture was concentrated by distillation under
19 reduced pressure, and treated with toluene. Solid obtained was collected and
20 dried in vacuo. 16.7 g of product was obtained. M. P. 138-141 °C

21 Reference Example 6: Preparation of m-(chlorosulfonyl)benzo-15-crown-5-
22 ether

23 To an ice-cold solution of benzo-15-crown-5-ether (536.6 mg, 2 mmole) in 5
24 ml of chloroform and cooled in ice-bath, 0.3 ml of chlorosulfonic acid (4.5
25 mmole) was slowly added. The reaction mixture was stirred in ice bath for 2
26 hr, then, 5 hr at room temperature. The reaction mixture was added to chopped
27 ice and extracted with dichloromethane (50 ml). Combined organic layer was
28 dried over magnesium chloride, and evaporated. 374 mg of product was

1 obtained. M.P. 79-84 °C

2 m-(Chlorosulfonyl)benzo-18-crown-6-ether was prepared using same method

3 as described above. Yield was about 46%. M. P. 108-110 °C

4 Reference Example 7: Preparation of 2-[p-(chlorosulfonyl)phenoxy]-N-(2-

5 pyridyl)acetamide

6 1.32 g of 2-(phenoxyacetyl)aminopyridine HCl salt (5 mmole) was

7 resuspended in 10 ml of dichloromethane and 2 ml of chlorosulfonic acid was

8 added in ice-bath to give clear solution. The solution was stirred at room

9 temperature for 3 hr. The reaction mixture was added to ice-water with good

10 stirring to give white solids. The solids were filtered, washed with acetonitrile,

11 and dried in vacuo. 0.65 g of solid was obtained. M. P. 170-175 °C

12 (decomposition)

13 Reference Example 8: Preparation of N-[p-(chlorosulfonyl)phenylmethyl]-

14 N,N-dimethylamine HCl salt

15 1.5 ml of N,N-dimethylbenzylamine (10 mmole) was dissolved in 6 ml of

16 dichloromethane and 2 ml of chlorosulfonic acid was added in ice bath

17 cooling. The reaction mixture was warmed to 40 °C for 40 min, and stirred at

18 room temperature for 1 hr. The reaction mixture was concentrated under

19 reduced pressure and poured into ice to give solids, which were collected and

20 dried in vacuo. 1.6 g (59.2%) of N-(p-chlorosulfonylphenylmethyl)-N,N-

21 dimethylamine HCl salt was obtained.

22 Reference Example 9: Preparation of 2-[p-(chlorosulfonyl)phenoxy]acetamide

23 3.0 g of 2-(phenoxy)acetamide was dissolved in 10 ml of dichloromethane and

24 6 ml of chlorosulfonic acid was slowly added at 0 °C. The reaction mixture

25 was stirred at room temperature for 10 hr. Dichloromethane was evaporated

26 under reduced pressure. Residual material was poured on chopped ice. Solid

27 was collected by filtration and dried in vacuo. 3.9 g of product was obtained.

28 M.P. 166-171 °C (decomposition)

1 Reference Example 10: Preparation of N-(p-chlorosulfonylphenylmethyl)
2 pyridinium chloride

3 p-(Chloromethyl)benzenesulfonyl chloride (2.2 g) was dissolved in acetonitrile
4 (20 ml)-dichloromethane (20 ml) and pyridine (1.9 ml) was added. The
5 reaction mixture was refluxed for 3 hr. Brown syrup was separated from
6 solvent, and was lyophilized in vacuo. Reddish brown product (2.9 g) was
7 obtained. M.P. 105-108 °C.

8 Reference Example 11: Preparation of p-(dimethylamino)benzenesulfonyl
9 chloride

10 N,N-Dimethylaniline (8 ml) was dissolved in 20 ml of chloroform, and
11 chlorosulfonic acid (20 ml) was slowly added with cooling. The reaction
12 mixture was refluxed for 6 hr. The reaction mixture was cooled and poured on
13 ice (100 g). Dichloromethane (120 ml) was added and aqueous layer was
14 neutralized by concentrated sodium carbonate solution with keeping
15 temperature below 4 °C. Organic layer was again washed with ice-cold 0.1 N
16 sodium bicarbonate solution, and dried over anhydrous magnesium sulfate.
17 Organic layer was concentrated under reduced pressure. Residual material was
18 crystallized from ethyl ether-heptane to give yellowish green solid. p-
19 (Dimethylamino)benzenesulfonyl chloride (4.2 g) was obtained. M. P. 108-
20 111 °C

21 Reference Example 12: Preparation of N-(carbamoylmethyl)-2-[4-
22 (chlorosulfonyl)phenoxy]acetamide

23 a) Preparation of N-(carbamoylmethyl)-2-(phenoxy)acetamide

24 Glycinamide HCl salt (5 g) was resuspended in 200 ml of dichloromethane
25 and 14 ml of triethylamine at 4 °C. Phenoxyacetyl chloride (6 ml) was slowly
26 added with good stirring. The reaction mixture was stirred at room temperature
27 for 3 hr, then, refluxed for 3 hr. The reaction mixture was cooled to give
28 crystalline solid, which was collected by filtration. Filtered solid was washed

1 with water, and dried in vacuo to give 7.5 g of product, N-(carbamoylmethyl)-
2 2-(phenoxy)acetamide . The filtrate was washed with water, and 0.1 N sodium
3 carbonate solution. The filtrate was concentrated, and treated with ether to
4 give additional product, 1.2 g of N-(carbamoylmethyl)-2-(phenoxy)acetamide .
5 M.P. 138-140 °C

6 b) Preparation of N-(carbamoylmethyl)-2-[4-
7 (chlorosulfonyl)phenoxy]acetamide

8 N-(carbamoylmethyl)-2-(phenoxy)acetamide (2.08 g) was resuspended in 30
9 ml of dichloromethane and chlorosulfonic acid (6 ml) was slowly added with
10 cooling. The reaction mixture was stirred at room temperature for 2 hr. Two
11 layers separated after standing for 10 min without stirring. Upper layer was
12 decanted. Lower layer was poured to chopped ice (60 g) with good mixing to
13 give white solid, which was collected by filtration and washed with ice-cold
14 water. The solid was dried in vacuo to give 2.78 g of N-(carbamoylmethyl)-2-
15 [4-(chlorosulfonyl)phenoxy]acetamide .
16 M.P. 97-100 °C (decomposition)

17

18 EXAMPLE 1

19 1-Benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
20 pyridyl)methylsulfinyl]-1H-benzimidazole and 1-Benzensulfonyl-6-methoxy-
21 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole

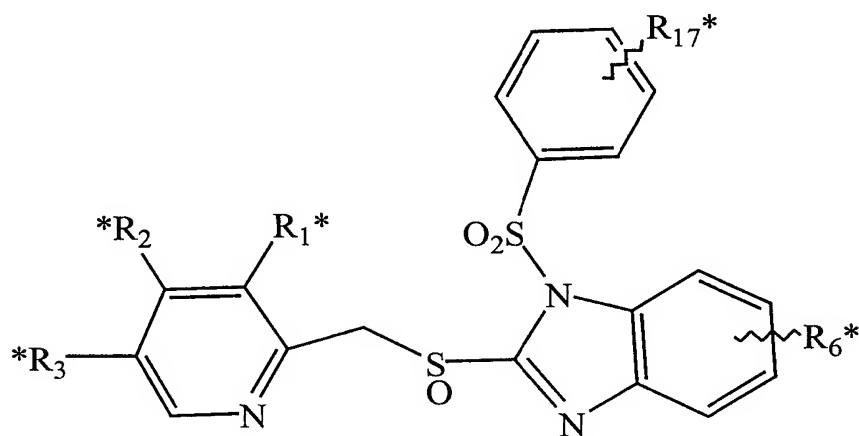
22 Method A: 5-Methoxy-2-[(3,5-dimethyl-4-methoxy-2-
23 pyridyl)methylsulfinyl]-1H-benzimidazole(172 mg, 0.5 mmole) was dissolved
24 in 20 ml of dichloromethane and 0.140 ml of triethylamine. The solution was
25 cooled to 0-4 °C in an ice bucket. Benzenesulfonyl chloride (96 mg, 0.55
26 mmole) was slowly added and stirred at 0-4 °C with thin layer chromatography
27 monitoring (developing solvent system: chloroform-methanol (10:1) and
28 acetonitrile-chloroform (1:1)). After the reaction was complete, the organic

1 layer was washed with an aqueous solution composed of 0.1 M NaCl, and 0.1
2 M sodium phosphate, pH 8.5. The organic layer was dried over anhydrous
3 magnesium sulfate and concentrated under reduced pressure. The residual
4 material was crystallized from dichloromethane-ethyl ether-heptane to provide
5 127 mg of product. M. p. 87-89 °C (decomposition). Heptane was introduced
6 to the remaining organic layer to provide a second crop of product (104 mg).
7 After combining the solids, 231 mg of the product (yield 95%) was obtained.
8 The product was composed of an mixture of 1-benzensulfonyl-5-methoxy-2-
9 [(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole and 1-
10 benzensulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
11 pyridyl)methylsulfinyl]-1H-benzimidazole (3:2 ratio by NMR)
12 ¹H NMR (CDCl₃, δ: 8.10-8.15 (m, 3H), 7.45-7.80(m, 5H), 7.0-7.1(m, 1H),
13 4.8-5.0(2q, 2AB total 2H), 3.83 and 3.92 (2s, total 3H), 3.75(s, 3H), 2.31(s,
14 3H), 2.23(s, 3H)
15 Method B: A mixture of 1-benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-
16 methoxy-2-pyridyl)methylthio]-1H-benzimidazole and 1-benzenesulfonyl-6-
17 methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylthio]-1H-
18 benzimidazole was prepared by reacting 5-methoxy-2-[(3,5-dimethyl-4-
19 methoxy-2-pyridyl)methylthio]-1H-benzimidazole with benzenesulfonyl
20 chloride as in method A. 1-Benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-
21 methoxy-2-pyridyl)methylthio]-1H-benzimidazole was isolated by silica gel
22 column chromatography and used in the next step as follows. 1-
23 Benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
24 pyridyl)methylthio]-1H-benzimidazole (318 mg, 1 mmole) in 30 ml of
25 dichloromethane was cooled to - 20 °C. A dichloromethane solution (5 ml)
26 containing m-chloroperbenzoic acid (equivalent to 1 mmole from 60% purity)
27 was slowly added. The reaction was monitored by thin layer chromatography.
28 After 5 hours the organic layer was washed with an aqueous solution of 0.1 M

1 sodium bicarbonate and 50 mM sodium thiosulfate. The organic layer was
2 dried over anhydrous magnesium sulfate and concentrated under reduced
3 pressure. Residual material was solidified from dichloromethane-ethyl ether-
4 heptane to provide 397 mg of product (yield 82%), 1-benzenesulfonyl-5-
5 methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-
6 benzimidazole and 1-benzenesulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-
7 2-pyridyl)methylsulfinyl]-1H-benzimidazole.

10 EXAMPLES 2-19

11 The compounds listed under Examples 2-19 below were prepared using the
12 method A as described in Example 1. 2-Pyridylmethylsulfinyl benzimidazole
13 compounds were reacted with the corresponding arylsulfonyl chloride to give
14 the corresponding 1-arylsulfonyl-2-pyridylmethylsulfinyl benzimidazoles as
15 shown in Table 1 with reference to **Formula 21**.



27 Formula 21

1

2

TABLE 1

| 3 | # | R ₆ * | R ₁ * | R ₂ * | R ₃ * | R ₁₇ * | Yield (%) | m.p. (°C) |
|----|-----------------|---------------------------------|------------------|----------------------------------|------------------|--------------------|-----------|-----------|
| 4 | 2 | 5-OCH ₃ ¹ | -CH ₃ | -OCH ₃ | -CH ₃ | 4-Cl | 81 | 76-78 |
| 5 | 3 | 5-OCH ₃ ¹ | -CH ₃ | -OCH ₃ | -CH ₃ | 4-Br | 73 | 84-86 |
| 6 | 4 | 5-OCH ₃ ¹ | -CH ₃ | -OCH ₃ | -CH ₃ | 4-F | 85 | 70-72 |
| 7 | 5 | 5-OCH ₃ ¹ | -CH ₃ | -OCH ₃ | -CH ₃ | 4-CH ₃ | 79 | 64-66 |
| 8 | 6 | 5-OCH ₃ | -CH ₃ | -OCH ₃ | -CH ₃ | 4-OCH ₃ | 83 | 85-87 |
| 9 | 7 | 5-OCH ₃ ¹ | -CH ₃ | -OCH ₃ | -CH ₃ | 3-CF ₃ | 67 | 65-67 |
| 10 | 8 | 5-OCH ₃ ¹ | -CH ₃ | -OCH ₃ | -CH ₃ | 4-OCF ₃ | 78 | 63-64 |
| 11 | 9 | H | -CH ₃ | OCH ₂ CF ₃ | H | H | 78 | 80-83 |
| 12 | 10 | H | -CH ₃ | OCH ₂ CF ₃ | H | 4-Cl | 79 | 90-92 |
| 13 | 11 | H | -CH ₃ | OCH ₂ CF ₃ | H | 4-Br | 71 | 105-107 |
| 14 | 12 | H | -CH ₃ | OCH ₂ CF ₃ | H | 4-F | 73 | 85-87 |
| 15 | 13 | H | -CH ₃ | OCH ₂ CF ₃ | H | 4-CH ₃ | 67 | 125-126 |
| 16 | 14 | H | -CH ₃ | OCH ₂ CF ₃ | H | 4-OCH ₃ | 78 | 94-95 |
| 17 | 15 | H | -CH ₃ | OCH ₂ CF ₃ | H | 3-CF ₃ | 67 | 123-125 |
| 18 | 16 | H | -CH ₃ | OCH ₂ CF ₃ | H | 4-OCF ₃ | 78 | 125-126 |
| 19 | 17 ² | 5-OCHF ₂ | OCH ₃ | OCH ₃ | H | H | 92 | 51-54 |
| 20 | 18 ² | 5-OCHF ₂ | OCH ₃ | OCH ₃ | H | 4-OCH ₃ | 87 | 67-69 |
| 21 | 19 ² | 5-OCHF ₂ | OCH ₃ | OCH ₃ | H | 4-OCF ₃ | 87 | 61-63 |

22 ¹ signifies a 3:2 ratio of 5-OCH₃ and 6-OCH₃23 ² signifies a 5:4 ratio of 5-OCHF₂ and 6-OCHF₂

1 EXAMPLE 20

2 5-Difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-
 3 benzimidazole, sodium salt sesquihydrate (432 mg, 1 mmole) was suspended in 30
 4 ml of dichloromethane in the presence of anhydrous sodium carbonate (100 mg).
 5 4-Chlorobenzenesulfonyl chloride (211 mg, 1 mmole) was added to the suspension
 6 and stirred at 4 °C overnight. The organic layer was separated by filtration and
 7 concentrated under reduced pressure. The residual solid was crystallized from
 8 dichloromethane-ethyl ether-heptane. 417 mg of isomer, 1-(4-
 9 chlorobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
 10 pyridyl)methylsulfinyl]-1H-benzimidazole and 1-(4-chlorobenzenesulfonyl)-6-
 11 difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole
 12 (5:4 ratio by NMR), was obtained. Yield 74.5% M.P. 82-83 °C.
 13 ¹H NMR (CDCl₃, δ: 8.05-8.15(m, 2H), 8.0(d, 1H), 7.78-7.81(m, 1H), 7.45-7.6(m,
 14 2H), 7.2-7.3(m, 1H), 6.80-6.81(d, 1H), 6.5-6.6(d, 1H), 4.9-5.0(q, 2H), 3.93(s, 3H).
 15

16 EXAMPLES 21-24

17 The compounds listed in Table 2, with reference to **Formula 20**, were prepared
 18 using the method described in Example 20.

19

20

TABLE 2

| 21 | % | R ₆ * | R ₁ * | R ₂ * | R ₃ * | R ₁₇ * | Yield(%) | m.p. (°C) |
|----|-----------------|---------------------|------------------|------------------|------------------|-------------------|----------|-----------|
| 22 | 21 ¹ | 5-OCHF ₂ | OCH ₃ | OCH ₃ | H | 4-Br | 87 | 80-82 |
| 23 | 22 ¹ | 5-OCHF ₂ | OCH ₃ | OCH ₃ | H | 4-F | 78 | 67-70 |
| 24 | 23 ¹ | 5-OCHF ₂ | OCH ₃ | OCH ₃ | H | 4-CH ₃ | 88 | 73-75 |
| 25 | 24 ¹ | 5-OCHF ₂ | OCH ₃ | OCH ₃ | H | 3-CF ₃ | 83 | 62-66 |

26 ¹ signifies a 5:4 ratio of 5-OCHF₂ and 6-OCHF₂

1 EXAMPLE 25

2 1-(Pyridine-3-sulfonyl)-5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-
3 pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(pyridine-3-sulfonyl)-6-
4 methoxy-2-[[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-
5 benzimidazole
6 5-Methoxy-2-[[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-
7 benzimidazole (344 mg) was dissolved in 20 ml of dichloromethane and 1 ml of
8 triethylamine. Pyridine-3-sulfonyl chloride (195 mg) was added and stirred in ice-
9 bath for 3 hr. Dichloromethane layer was washed with an aqueous solution
10 composed of 0.1 M NaCl and 0.1 M sodium bicarbonate. Dichloromethane layer
11 was dried over anhydrous magnesium sulfate. Solvent was removed under reduced
12 pressure. Residual material was precipitated by dichloromethane-ethyl ether-
13 heptane to provide 372 mg of product, which were a mixture of 1-(pyridine-3-
14 sulfonyl)-5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-
15 benzimidazole and 1-(pyridine-3-sulfonyl)-6-methoxy-2-[[3,5-dimethyl-4-
16 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (3:1 ratio by NMR).
17 M.P. 136-138 °C (decomposition)
18 NMR (CDCl₃, δ): 2.27 (s, 3H), 2.35 (s, 3H), 3.82 (s, 3H), 3.86 & 3.93 (2s, total
19 3H), 5.04-5.17 (q, AB, 2H), 7.01-7.02 (dd, 1H), 7.47-7.56 (m, 2H), 7.67-7.71 (d,
20 1H), 8.15 (s, 1H), 8.51-8.55 (dd, 1H), 8.85-8.88 (d, 1H), 9.34 (s, 1H)

21

22 EXAMPLE 26

23 1-(Pyridine-3-sulfonyl)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
24 pyridyl)methyl]sulfinyl]-1H-benzimidazole
25 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-
26 benzimidazole (370 mg) was dissolved in 20 ml of dichloromethane and 1 ml of
27 triethylamine. Pyridine-3-sulfonyl chloride (195 mg) was added and stirred in ice-
28 bath for 5 hr. Dichloromethane layer was washed with an aqueous solution

1 composed of 0.1 M NaCl and 0.1 M sodium bicarbonate. Dichloromethane layer
2 was dried over anhydrous magnesium sulfate. Solvent was removed under reduced
3 pressure. Residual material was precipitated by dichloromethane-ethyl ether-
4 heptane to provide 348 mg of 1-(pyridine-3-sulfonyl)-2-[(3-methyl-4-(2,2,2-
5 trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole.

6 M.P. 118-120 °C (decomposition)

7 NMR (CDCl₃, δ): 2.35 (s, 3H), 4.38-4.49 (q, 2H), 4.98-5.22 (q, AB, 2H), 6.73 (d,
8 1H), 7.41-7.56 (m, 3H), 7.80-8.02 (dd, 2H), 8.23 (s, 1H), 8.52 (dd, 1H), 8.87 (dd,
9 1H), 9.36 (s, 1H)

10

11 EXAMPLE 27

12 1-(Pyridine-3-sulfonyl)-5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
13 pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(pyridine-3-sulfonyl)-6-
14 (difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-
15 benzimidazole

16 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-
17 benzimidazole (383 mg) was dissolved in 20 ml of dichloromethane and 1 ml of
18 triethylamine. Pyridine-3-sulfonyl chloride (195 mg) was added and stirred in ice-
19 bath for 5 hr. Dichloromethane layer was washed with an aqueous solution
20 composed of 0.1 M NaCl and 0.1 M sodium bicarbonate. Dichloromethane layer
21 was dried over anhydrous magnesium sulfate. Solvent was removed under reduced
22 pressure. Residual material was precipitated by dichloromethane-ethyl ether-
23 heptane to provide 397 mg of a mixture of 1-(pyridine-3-sulfonyl)-5-
24 (difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-
25 benzimidazole and 1-(pyridine-3-sulfonyl)-6-(difluoromethoxy)-2-[(3,4-
26 dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (ratio 3:2 by NMR).

27 M.P. 127-128 °C (decomposition)

28

1 EXAMPLE 28

2 Preparation of 1-(morpholin-4-yl)phenylsulfonyl-5-methoxy-2-[(3,5-dimethyl-4-
3 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(morpholin-4-
4 yl)phenylsulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
5 pyridyl)methyl]sulfinyl]-1H-benzimidazole

6 270.8 mg of 4-(p-chlorosulfonyl)phenyl morpholine was added to 344 mg of 5-
7 Methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-
8 benzimidazole in 20 ml of dichloromethane and 0.5 ml of triethylamine. The
9 reaction mixture was stirred at room temperature overnight. Dichloromethane layer
10 was washed with water, and dried over anhydrous magnesium sulfate. Organic
11 layer was evaporated. Residual material was lyophilized in vacuo to give 425 mg
12 of the titled product (1:1 ratio by NMR).

13 m.p.; 76-79 °C (decomposition)

14

15 EXAMPLE 29

16 Preparation of N-[4-[[5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
17 pyridyl)methyl]sulfinyl]benzimidazol-1-yl]sulfonyl]phenyl]urea and N-[4-[[6-
18 methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]benzimidazol-1-
19 yl]sulfonyl]phenyl]urea

20 128 mg of N-[4-(chlorosulfonyl)phenyl]urea was added to 172 mg of 5-Methoxy-
21 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole in a
22 mixture of 0.5 ml of triethylamine and 10 ml of dichloromethane-acetonitrile
23 (50/50). The reaction mixture was stirred at room temperature overnight.
24 Dichloromethane (20 ml) was added and washed with water, and 0.1 M sodium
25 bicarbonate solution. Organic layer was dried over anhydrous magnesium sulfate
26 and evaporated. Residue was dissolved in 2 ml of dichloromethane and ethyl ether
27 was added for crystallization. Crystals were collected and dried. 190 mg of product
28 was obtained. The product was composed of a mixture of N-[4-[[5-methoxy-2-

1 [[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]benzimidazol-1-
2 yl)sulfonyl]phenyl]urea and N-[4-[[6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
3 pyridyl)methyl]sulfinyl]benzimidazol-1-yl)sulfonyl]phenyl]urea (4:3 ratio by
4 NMR).

5 m.p.; 154-158 °C (decomposition)

6 NMR (CDCl₃, δ): 2.19 (s, 3H), 2.20 & 2.21 (2s, total 3H), 3.69 & 3.70 (2s, total
7 3H), 3.76 & 3.89 (2s, total 3H), 4.75-4.94 (q, AB, 2H), 5.6-5.7 (br, NH₂), 6.95-
8 7.08 (d, 1H), 7.05 (s, 1H), 7.43-7.86 (m, 5H), 8.12 (s, 1H), 9.0 (br, NH)

9

10 EXAMPLE 30

11 Preparation of N-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
12 pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenyl)urea

13 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

14 benzimidazole (185 mg) dissolved in 30 ml of dichloromethane and 0.4 ml of
15 triethylamine was added to 128 mg of N-[4-(chlorosulfonyl)phenyl]urea. The
16 reaction mixture was stirred at room temperature overnight. The reaction mixture
17 was washed with water and 0.1 N sodium bicarbonate solution. Organic layer was
18 dried over anhydrous magnesium sulfate, and concentrated under reduced
19 pressure. Residue was dissolved in 2 ml of dichloromethane and ethyl ether was
20 added for precipitation. 125 mg of the titled product was obtained.

21 M.P. 115 °C (decomposition)

22 NMR (CDCl₃, δ): 2.25 (s, 3H), 4.37-4.42 (q, 2H), 4.6-4.85 (q, AB, 2H), 6.67 (d,
23 1H), 7.35-7.42 (m, 2H), 7.61-7.75 (m, 3H), 7.89-8.05 (m, 2H), 8.27-8.38 (m, 2H)

24

25 EXAMPLE 31

26 Preparation of 15-[(5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-
27 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]-

28 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene and 15-[(6-

1 methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimidazol-1-
2 yl)sulfonyl]- 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
3 170 mg of 5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-
4 1H-benzimidazole
5 and 190 mg of m-(chlorosulfonyl) benzo-15-crown-5-ether were dissolved in 0.2
6 ml of triethylamine and 20 ml of dichloromethane. The reaction mixture was
7 stirred at room temperature overnight. Organic layer was washed with water and
8 dried over anhydrous magnesium sulfate. Solvent was removed to give syrup,
9 which was lyophilized. 210 mg of the titled product, a mixture of 15-[(5-methoxy-
10 2-{[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimidazol-1-
11 yl)sulfonyl]- 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene and
12 15-[(6-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-
13 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]-
14 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene (1:1 ratio by
15 NMR), was obtained. Lyophilized product showed M.P. 76-80 °C with
16 decomposition.
17 NMR (CDCl₃, δ): 2.21 (s, 3H), 2.31 (s, 3H), 3.68-3.73 (m, 8H), 3.74 (s, 3H), 3.84-
18 3.87 (m, 4H), 3.90 (s, 3H), 4.10-4.13 (m, 4H), 4.81-4.95 (2q, 2AB, 2H), 6.84 (d,
19 1H), 7.00-7.07 (dd, 1H), 7.25 (d, 1H), 7.42-7.72 (m, 3H), 8.15 (s, 1H)
20

21 EXAMPLE 32

22 Preparation of 15-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
23 pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}-
24 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
25 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-
26 benzimidazole (185 mg) dissolved in 20 ml of dichloromethane and 0.2 ml of
27 triethylamine was added to 190 mg of m-(chlorosulfonyl) benzo-15-crown-5-ether.
28 The reaction mixture was stirred at room temperature overnight. Organic layer was

1 washed with water and dried over anhydrous magnesium sulfate. Solvent was
2 removed to give syrup, which was lyophilized. 231 mg of the titled product was
3 obtained. Lyophilized product showed M.P. 76-80 °C with decomposition.
4 NMR (CDCl₃, δ): 2.33 (s, 3H), 3.66-3.73 (m, 8H), 3.83-3.87 (m, 4H), 4.10-4.12
5 (m, 4H), 4.35-4.41 (q, 2H), 4.84-5.05 (q, AB, 2H), 6.61 (d, 1H), 6.86 (d, 1H),
6 7.37-7.45 (m, 2H), 7.56 (s, 1H), 7.71-7.74 (dd, 2H), 7.95 (d, 1H), 8.23 (d, 1H)

7

8 EXAMPLE 33

9 Preparation of 2-{4-[(5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
10 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
11 pyridyl)acetamide and 2-{4-[(6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
12 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
13 pyridyl)acetamide

14 170 mg of 2-[p-(chlorosulfonyl)phenoxy]-N-(2-pyridyl)acetamide was added to
15 172 mg of 5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-
16 1H-benzimidazole dissolved in dichloromethane (15 ml) and triethylamine (0.4
17 ml). The reaction mixture was stirred at room temperature overnight. The reaction
18 mixture was washed with water. Organic layer was dried over anhydrous
19 magnesium sulfate, and evaporated. Residual material was lyophilized in vacuo to
20 give 244 mg of the titled product, which was a mixture of 2-{4-[(5-methoxy-2-
21 {[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-
22 yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide and 2-{4-[(6-methoxy-2-[(3,5-
23 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-
24 yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide (2:1 ratio by NMR).
25 M.P. 76-80 °C
26 NMR (CDCl₃, δ): 2.21 & 2.23 (2s, total 3H), 2.32 (s, 3H), 3.74 & 3.75 (2s, total
27 3H), 3.83 & 3.93 (2s, total 3H), 4.65 (s, 2H), 4.83-4.92 (q, AB, 2H), 6.99-7.11 (m,
28 5H), 7.46 (d, 1H), 7.68-7.88 (m, 2H), 8.75 (br, NH)

1 EXAMPLE 34

2 Preparation of 2-(4-{[2-([3-methyl-4-(2,2,2-trifluoroethoxy)-2-3 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl}phenoxy)-N-(2-4 pyridyl)acetamide

5 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-

6 benzimidazole (185 mg) dissolved in 20 ml of dichloromethane and 0.2 ml of

7 triethylamine was added to 170 mg of 2-[p-(chlorosulfonyl)phenoxy]-N-(2-

8 pyridyl)acetamide. The reaction mixture was washed with water. Organic layer

9 was dried over anhydrous magnesium sulfate, and evaporated. Residual material

10 was lyophilized to give 237 mg of the titled product. M.P. 78-81 °C.

11 NMR (CDCl₃, δ): 2.31 (s, 3H), 4.34-4.40 (q, 2H), 4.71 (s, 2H), 4.84-5.05 (q, AB,

12 2H), 6.62 (d, 1H), 7.09 (d, 2H), 7.29-7.47 (m, 2H), 7.62-7.80 (m, 2H), 7.98 (d,

13 1H), 8.11 (d, 2H), 8.20-8.29 (m, 4H), 8.92 (br, NH)

14

15 EXAMPLE 35

16 Preparation of 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-17 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-18 pyridyl)acetamide and 2-{4-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-19 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-20 pyridyl)acetamide

21 5-(difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-

22 benzimidazole (192 mg) dissolved in 20 ml of dichloromethane and 0.2 ml of

23 triethylamine was added to 170 mg of 2-[(p-

24 chlorosulfonyl)phenoxyacetyl]aminopyridine. The reaction mixture was washed

25 with water. Organic layer was dried over anhydrous magnesium sulfate, and

26 evaporated. Residual material was lyophilized to give 187 mg of the titled product,

27 which was a mixture of 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-

28 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-

1 pyridyl)acetamide and 2-{4-[(6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
2 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
3 pyridyl)acetamide (2:1 ratio by NMR).
4 M.P. 95-101 °C
5 NMR (CDCl₃, δ): 3.90 (s, 3H), 3.93 (s, 3H), 4.67 (s, 2H), 4.85-5.00 (2q, 2AB, 2H;
6 s like, 1H), 6.52-6.80 (m, 2H), 7.08 (m, 3H), 7.29-7.40 (d, 1H), 7.58-7.80 (m, 2H),
7 7.97-8.16 (m, 3H), 8.22 (d, 1H), 8.30 (d, 1H), 8.82 (br, NH)

8

9 EXAMPLE 36

10 Preparation of 1-[4-(3-(morpholin-4-yl) propoxy) benzenesulfonyl]-5-
11 (difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-
12 benzimidazole and 1-[4-(3-(morpholin-4-yl) propoxy) benzenesulfonyl]-6-
13 (difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-
14 benzimidazole

15 180 mg of 4-(3-(morpholin-4-yl) propoxy) benzenesulfonyl chloride was added to
16 a solution of 190 mg of 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
17 pyridyl)methyl]sulfinyl]-1H-benzimidazole in 10 ml of dichloromethane and 0.5
18 ml of triethylamine. The reaction mixture was stirred overnight, and washed with
19 water. Organic layer was concentrated and lyophilized in vacuo. 210 mg of the
20 titled mixture was obtained (1:1 ratio by NMR).

21

22 EXAMPLE 37

23 Preparation of 1-[4-[3-(morpholin-4-yl) propoxy] benzenesulfonyl]-5-methoxy-2-
24 [(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[
25 4-[3-(morpholin-4-yl) propoxy] benzenesulfonyl]-6-methoxy-2-[(3,5-dimethyl-4-
26 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

27 200 mg of 4-[3-(morpholin-4-yl) propoxy] benzenesulfonyl chloride was added to
28 a solution of 200 mg of 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

1 pyridyl)methyl]sulfinyl]-1H-benzimidazole in 10 ml of dichloromethane and 0.5
2 ml of triethylamine. The reaction mixture was stirred overnight, and washed with
3 water. Organic layer was concentrated and treated with ethyl ether to give solids.
4 Solids were crystallized from dichloromethane and ether. 210 mg of the titled
5 product, 1:1 ratio of 5-methoxy and 6-methoxy compound, was obtained.
6 M.P. 98-102 °C (decomposition)
7 NMR (CDCl₃, δ): 1.97-2.05 (m, 2H), 2.09 (s, 3H), 2.20 (s, 3H) 3.05-3.15 (m, 6H),
8 3.58 (s, 3H), 3.65-3.80 (m, 4H), 3.81 & 3.92 (2s, total 3H), 3.82-3.95 (t, 2H), 4.73-
9 4.94 (q, AB, 2H), 6.89-6.91 (d, 2H), 7.4-7.6 (m, 3H), 7.79-8.0 (m, 2H), 8.17 (s,
10 1H)

11

12 EXAMPLE 38

13 Preparation of 1-[(N,N-dimethylamino)methyl]benzene-4-sulfonyl]-5-methoxy-2-
14 [(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-
15 [(N,N-dimethylamino)methyl]benzene-4-sulfonyl]-6-methoxy-2-[(3,5-dimethyl-
16 4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

17 120 mg of N-[p-(chlorosulfonyl)phenyl]methyl]-N,N-dimethylamine was added
18 to 172 mg of 5-Methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-
19 1H-benzimidazole dissolved in 20 ml of dichloromethane and 0.5 ml of
20 triethylamine. The reaction mixture was stirred at room temperature for 16 hr.
21 Dichloromethane layer was washed with water, and 0.1 N sodium bicarbonate
22 solution. The organic layer was dried over anhydrous magnesium sulfate and
23 concentrated under reduced pressure. Residual material was lyophilized in vacuo
24 to give 245 mg of the titled product (1:1 ratio by NMR).

25

26 EXAMPLE 39

27 Preparation of 1-[2-acetamido-4-methyl-5-thiazolylsulfonyl]-5-methoxy-2-[(3,5-
28 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

1 172 mg of 5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-
2 1H-benzimidazole was dissolved in 10 ml of dichloromethane and 0.4 ml of
3 triethylamine, and 128 mg of 2-acetamido-4-methyl-5-thiazolyl sulfonyl chloride
4 was added. The reaction mixture was stirred at room temperature for 15 hr.
5 Product spot was shown at slightly higher position than 5-methoxy-2-[[[(3,5-
6 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole in thin layer
7 chromatography (developing solvent: dichloromethane-acetonitrile-methanol =
8 100:10:5). Product was separated by silica gel column chromatography. 145 mg of
9 the titled product was isolated.

10

11 EXAMPLE 40

12 Preparation of 1-(thiophene-2-sulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-
13 2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(thiophene-2-sulfonyl)-6-
14 methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-
15 benzimidazole

16 172 mg of 5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-
17 1H-benzimidazole was dissolved in 10 ml of dichloromethane and 0.2 ml of
18 triethylamine. 95 mg of thiophene-2-sulfonyl chloride was added. . The reaction
19 mixture was stirred at room temperature for 16 hr. Dichloromethane layer was
20 washed with water and concentrated under reduced pressure. Residual material
21 was crystallized from acetonitrile-ethyl ether-hexane. 225 mg of the titled product,
22 a mixture of 1-(thiophene-2-sulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
23 pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(thiophene-2-sulfonyl)-6-
24 methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-
25 benzimidazole (7:1 ratio by NMR), was obtained.

26 M.P. 86-90 °C

27 NMR (CDCl₃, δ): 2.20 (s, 3H), 2.30 (s, 3H), 3.73 (s, 3H), 3.83 & 3.91 (2s, total
28 3H), 4.80-4.92 (q, AB, 2H), 7.00-7.10 (m, 2H), 7.47 (s, 1H), 7.67-7.69 (m, 2H),

1 7.97-7.99 (d, 1H), 8.13 (s, 1H)

2

3 EXAMPLE 41

4 Preparation of 1-(phenylmethylsulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-
5 2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(phenylmethylsulfonyl)-6-
6 methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-
7 benzimidazole

8 172 mg of 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-
9 1H-benzimidazole was dissolved in 10 ml of dichloromethane and 0.2 ml of
10 triethylamine. 95 mg of phenylmethylsulfonyl chloride was added. . The reaction
11 mixture was stirred at room temperature for 36 hr. Dichloromethane layer was
12 washed with water and concentrated under reduced pressure. Residual material
13 was lyophilized in vacuo to give 205 mg of the titled product, a mixture of 1-
14 (phenylmethylsulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
15 pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(phenylmethylsulfonyl)-6-
16 methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-
17 benzimidazole (2:1 ratio by NMR)
18 M.P. 130 °C (decomposition)

19

20 EXAMPLE 42

21 Preparation of 1-(n-propanesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
22 pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(n-propanesulfonyl)-6-methoxy-
23 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

24 103 mg of 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-
25 1H-benzimidazole was dissolved in 2 ml of chloroform and 0.1 ml of
26 triethylamine. 1-Propanesulfonyl chloride (0.042 ml) was slowly added in ice bath.
27 The reaction mixture was stirred at room temperature for 3 hr. Organic layer was
28 washed with cold 0.1 N sodium bicarbonate solution. Chloroform layer was dried

1 over anhydrous magnesium sulfate, and concentrated under reduced pressure.
2 Residual material was solidified from chloroform-ethyl ether-hexane to give 128
3 mg (95%) of the titled product (3:2 ratio).
4 M.P. 96-100 °C

5

6 EXAMPLE 43

7 Preparation of 1-(n-butanesulfonyl)-5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-
8 pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(n-butanesulfonyl)-6-methoxy-
9 2-[[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

10 103 mg of 5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-
11 1H-benzimidazole was dissolved in 2 ml of chloroform and 0.1 ml of
12 triethylamine. 1-Butanesulfonyl chloride (0.042 ml) was slowly added in ice bath.
13 The reaction mixture was stirred at room temperature for 3 hr. Organic layer was
14 washed with cold 0.1 N sodium bicarbonate solution. Chloroform layer was dried
15 over anhydrous magnesium sulfate, and concentrated under reduced pressure.
16 Residual material was solidified from chloroform-ethyl ether-hexane to give 130
17 mg (93%) of the titled product (3:2 ratio).
18 M.P. 54-56 °C

19

20 EXAMPLE 44

21 Preparation of 1-(isopropylsulfonyl)-5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-
22 pyridyl)methyl]sulfinyl]-1H-benzimidazole and -(isopropylsulfonyl)-6-methoxy-2-
23 [[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

24 103 mg of 5-methoxy-2-[[3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-
25 1H-benzimidazole was dissolved in 2 ml of chloroform and 0.1 ml of
26 triethylamine. Isopropylsulfonyl chloride (0.042 ml) was slowly added in ice bath.
27 The reaction mixture was stirred at room temperature for 24 hr. Organic layer was
28 concentrated under reduced pressure and applied to silica gel column

1 chromatography. 78 mg of the titled product was isolated (1:1 ratio).

2 M.P. 105-108 °C (decomposition)

3

4 EXAMPLE 45

5 1-[(N,N-dimethylamino)benzene-4-sulfonyl]-5-methoxy-2-[(3,5-dimethyl-4-
6 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[(N,N-
7 dimethylamino)benzene-4-sulfonyl]-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
8 pyridyl)methyl]sulfinyl]-1H-benzimidazole

9 120 mg of p-(N,N-dimethylamino)benzenesulfonyl chloride was added to 172 mg
10 of 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-
11 benzimidazole dissolved in 20 ml of dichloromethane and 0.5 ml of triethylamine.
12 The reaction mixture was stirred at room temperature for 16 hr. Dichloromethane
13 layer was washed with water and 0.1 N sodium carbonate solution. Organic layer
14 was dried over anhydrous magnesium sulfate and was concentrated under reduced
15 pressure. Residual material was lyophilized in vacuo to give 215 mg of the titled
16 product (1:1 ratio).

17 M.P. 92-96 °C

18 NMR (CDCl₃, δ): 2.24 (s, 3H), 2.30 (s, 3H), 3.02 (s, 3H), 3.03 (s, 3H), 3.75 (s,
19 3H), 3.83 & 3.92 (2s, total 3H), 4.77-4.94 (2q, AB & A'B', total 2H), 6.57-6.61
20 (m, 2H), 6.96-7.07 (m, 1H), 7.48 & 7.68 (2d, total 1H), 7.85-7.90 (m, 3H), 8.22 (s,
21 1H)

22

23 EXAMPLE 46

24 Preparation of N-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-
25 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenyl)urea

26 128 mg of N-[4-(chlorosulfonyl)phenyl]urea was added to 191 mg of 2-[(3-
27 methyl-4-methoxypropoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole sodium
28 salt in a mixture of 0.1 ml of triethylamine and 10 ml of dichloromethane-

1 acetonitrile (50/50). The reaction mixture was stirred at room temperature
2 overnight. Dichloromethane (20 ml) was added and washed with water, and 0.1 M
3 sodium bicarbonate solution. Organic layer was dried over anhydrous magnesium
4 sulfate and evaporated. Residue was dissolved in minimum amounts of acetonitrile
5 and ethyl ether was added for crystallization. Crystals were collected and dried.
6 190 mg of the titled product was obtained.
7 NMR (CDCl₃, δ): 2.03-2.07 (m, 2H), 2.18 (s, 3H), 3.34 (s, 3H), 3.52-3.54 (t, 2H),
8 4.05-4.08 (t, 2H), 4.76-5.00 (q, AB, 2H), 5.50-5.61 (br, -NH₂), 6.69 (d, 1H), 7.33-
9 7.37 (m, 3H), 7.51 (d, 1H), 7.65 (d, 1H), 7.81 (d, 2H), 7.98 (d, 1H), 8.17 (d, 1H),
10 8.97 (s, -NH-)

11

12 EXAMPLE 47

13 Preparation of 1-(pyridine-3-sulfonyl)-2-[[[3-methyl-4-(3-methoxypropoxy)-2-
14 pyridyl]methyl]sulfinyl]-1H-benzimidazole

15 100 mg of pyridine-3-sulfonyl chloride was added to 191 mg of 2-[[[3-methyl-4-
16 (3-methoxypropoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium salt in
17 a mixture of 0.15 ml of triethylamine and 10 ml of dichloromethane. The reaction
18 mixture was stirred at room temperature overnight. Dichloromethane (20 ml) was
19 added and washed with water, and 0.1 M sodium bicarbonate solution. Organic
20 layer was dried over anhydrous magnesium sulfate and evaporated. Residue was
21 dissolved in minimum amounts of acetonitrile and ethyl ether was added for
22 precipitation. Solids was collected and dried to give 127 mg of the titled product.
23 NMR (CDCl₃, δ): 1.97-2.10 (m, 2H), 2.21 (s, 3H), 3.35 (s, 3H), 3.51-3.57 (t, 2H),
24 4.04-4.07 (t, 2H), 4.82-5.14 (q, AB, 2H), 6.73 (d, 1H), 7.41-7.56 (m, 3H), 7.80-
25 8.02 (dd, 2H), 8.23-8.87 (m, 3H), 9.34 (s, 1H)

26

27 EXAMPLE 48

28 Preparation of 2-(4-{[2-(4-(3-methoxypropoxy)-3-methyl-2-

1 pyridyl)methyl}sulfinyl)benzimidazol-1-yl)sulfonyl}phenoxy)-N-(2-
2 pyridyl)acetamide

3 170 mg of 2-[p-(chlorosulfonyl)phenoxy]-N-(2-pyridyl)acetamide was added to
4 191 mg of 2-[[[4-(3-methoxypropoxy)-3-methyl-2- pyridyl)methyl}sulfinyl]-1H-
5 benzimidazole sodium salt in dichloromethane (15 ml) and triethylamine (0.1 ml).
6 The reaction mixture was stirred at room temperature overnight. The reaction
7 mixture was washed with water. Organic layer was dried over anhydrous
8 magnesium sulfate, and evaporated. Residual material was lyophilized in vacuo to
9 give 244 mg of the titled product.

10 M.P. 78-81 °C (decomposition)

11 NMR (CDCl₃, δ): 2.00-2.10 (m, 2H), 2.27 (s, 3H), 3.35 (s, 3H), 3.52-3.57 (t, 2H),
12 4.06-4.10 (t, 2H), 4.64 (s, 2H), 4.83-5.02 (q, AB, 2H), 6.67 (d, 1H), 7.07-7.10 (m,
13 3H), 7.32-7.49 (m, 3H), 7.70-7.82 (m, 2H), 7.99 (d, 1H), 8.14-8.30 (m, 4H), 8.77
14 (br, NH)

15

16 EXAMPLE 49

17 Preparation of 1-[4-(morpholin-4-yl)phenylsulfonyl]-2-[[[4-(3-methoxypropoxy)-
18 3-methyl-2-pyridyl)methyl}sulfinyl]-1H-benzimidazole

19 136 mg of 4-[(p-chlorosulfonyl)phenyl] morpholine was added to 191 mg of 2-
20 [[[4-(3-methoxypropoxy)-3-methyl -2-pyridyl)methyl}sulfinyl]-1H-benzimidazole
21 sodium salt in dichloromethane (15 ml) and triethylamine (0.1 ml). The reaction
22 mixture was stirred at room temperature overnight. The reaction mixture was
23 washed with water. Organic layer was dried over anhydrous magnesium sulfate,
24 and evaporated. Residual material was lyophilized in vacuo to give 224 mg of the
25 titled product.

26 M.P. 93-96 °C (decomposition)

27 NMR (CDCl₃, δ): 2.02-2.06 (m, 2H), 2.26 (s, 3H), 3.2-3.3 (m, 4H), 3.35 (s, 3H),
28 3.50-3.53 (t, 2H), 3.75-3.80 (m, 4H), 4.04-4.08 (t, 2H), 4.71-4.79 (q, AB, 2H),

1 6.71 (d, 1H), 7.26-7.5 (m, 4H), 7.8-8.1 (m, 2H), 8.27 (d, 1H)

2

3 EXAMPLE 50

4 Preparation of 1-[[2-(morpholin-4-yl)ethoxy]phenyl-4-sulfonyl]-2-[[[4-(3-
5 methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole

6 136 mg of 4-[2-[(p-chlorosulfonyl)phenoxy]ethyl]morpholine was added to 191

7 mg of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-

8 benzimidazole sodium salt in dichloromethane (15 ml) and triethylamine (0.1 ml).

9 The reaction mixture was stirred at room temperature overnight. The reaction

10 mixture was washed with water. Organic layer was dried over anhydrous

11 magnesium sulfate, and evaporated. Residual material was lyophilized in vacuo to

12 give 234 mg of the titled product.

13 NMR (CDCl₃, δ): 2.05-2.10 (m, 2H), 2.27 (s, 3H), 2.56 (m, 4H), 2.79-2.82 (t, 2H),

14 3.35 (s, 3H), 3.53-3.56 (t, 2H), 3.69-3.72 (m, 4H), 4.07-4.10 (t, 2H), 4.12-4.15 (t,

15 2H), 4.81-4.99 (q, AB, 2H), 6.68 (d, 1H), 6.95 (d, 2H), 7.36-7.46 (m, 2H), 7.81 (d,

16 1H), 7.99 (d, 1H), 8.06 (d, 2H), 8.21 (d, 1H)

17

18 EXAMPLE 51

19 Preparation of 1-(thiophene-2-sulfonyl)-2-[[[4-(3-methoxypropoxy)-3-methyl-2-
20 pyridyl]methyl]sulfinyl]-1H-benzimidazole

21 92 mg of thiophene-2-sulfonyl chloride was added to 191 mg of 2-[[[4-(3-

22 methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium

23 salt in dichloromethane (15 ml) and triethylamine (0.1 ml). The reaction mixture

24 was stirred at room temperature overnight. The reaction mixture was washed with

25 water. Organic layer was dried over anhydrous magnesium sulfate, and

26 evaporated. Residual material was lyophilized in vacuo to give 215 mg of the titled

27 product.

28 M.P. 147-150 °C

1 NMR (CDCl₃, δ): 2.00-2.08 (m, 2H), 2.27 (s, 3H), 3.35 (s, 3H), 3.53-3.56 (s, 3H),
2 4.07-4.10 (t, 2H), 4.83-5.00 (q, AB, 2H), 6.67 (d, 1H), 7.08-7.10 (t, 1H), 7.42-7.49
3 (m, 2H), 7.68-7.70 (d, 1H), 7.82-7.84 (d, 1H), 8.00-8.03 (m, 2H), 8.18 (d, 1H)

4
5 EXAMPLE 52

6 Preparation of 1-benzenesulfonyl-2-[[[4-(3-methoxypropoxy)-3-methyl-2-
7 pyridyl]methyl]sulfinyl]-1H-benzimidazole

8 94 mg of benzenesulfonyl chloride was added to 191 mg of 2-[[[4-(3-
9 methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium
10 salt in dichloromethane (15 ml) and triethylamine (0.1 ml). The reaction mixture
11 was stirred at room temperature overnight. The reaction mixture was washed with
12 water. Organic layer was dried over anhydrous magnesium sulfate, and
13 evaporated. Residual material was crystallized from acetonitrile-ethyl ether. 210
14 mg of the titled product was obtained.

15 M.P. 126-128 °C

16 NMR (CDCl₃, δ): 1.97-2.09 (m, 2H), 2.27 (s, 3H), 3.34 (s, 3H), 3.52-3.57 (t, 3H),
17 4.05-4.10 (t, 3H), 4.81-5.03 (q, AB, 2H), 6.66 (d, 1H), 7.38-7.53 (m, 4H), 7.61-
18 7.65 (t, 1H), 7.80 (d, 1H), 8.00 (d, 1H), 8.11-8.16 (m, 3H)

19
20 EXAMPLE 53

21 Preparation of 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
22 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide and 2-{4-
23 [(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
24 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide

25 5-Methoxy-2-[[[4-(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-
26 benzimidazole (344 mg) was dissolved in 40 ml of dichloromethane and 1 ml of
27 triethylamine. 2-[p-(chlorosulfonyl)phenoxy]acetamide (250 mg) was added. The
28 reaction mixture was stirred at room temperature overnight. The reaction was

1 monitored by thin layer chromatography (developing solvent: chloroform-
2 acetonitrile-methanol (100:10:7)). Solid was collected by filtration, washed with
3 small amounts of dichloromethane, and dried in vacuo to give 415 mg of the titled
4 product (3:2 ratio of 5-methoxy / 6-methoxy compound).

5 M.P. 159-161 °C (decomposition)

6 NMR (DMSO-d₆, δ): 2.13 (s, 3H), 2.25 (s, 3H), 3.69 (s, 3H), 3.78 & 3.88 (2s,
7 total 3H), 4.56 (s, 2H), 4.82-5.04 (2q, AB, 2H), 7.05-7.18 (m, 3H), 7.34-7.40 (m,
8 1H), 7.60-7.90 (m, 2H), 8.12-8.18 (m, 2H)

9
10 EXAMPLE 54

11 Preparation of 2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
12 pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)acetamide
13 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-
14 benzimidazole (370 mg) was dissolved in 20 ml of dichloromethane and 1 ml of
15 triethylamine. 2-[p-(chlorosulfonyl)phenoxy]acetamide(250 mg) was added. The
16 reaction mixture was stirred at room temperature for 24 hr. Solid was collected,
17 washed with dichloromethane, and dried in vacuo. 378 mg of the titled product
18 was obtained.

19 M.P. 162-166 °C (decomposition)

20 NMR (DMSO-d₆, δ): 2.21 (s, 3H), 4.55 (s, 2H), 4.86-5.15 (q, 2H and q, 2H) 6.99
21 (d, 1H), 7.16 (d, 2H), 7.39-7.58 (m, 2H), 7.79 (d, 1H), 7.97-8.03 (m, 2H), 8.17 (d,
22 2H)

23
24 EXAMPLE 55

25 Preparation of 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-
26 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide and 2-{4-
27 [(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-
28 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide

1 5-(difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-
2 benzimidazole (383 mg) was dissolved in 20 ml of dichloromethane and 1 ml of
3 triethylamine. 2-[p-(chlorosulfonyl)phenoxy]acetamide(250 mg) was added. The
4 reaction mixture was stirred at room temperature for 24 hr. Solid was collected,
5 washed with dichloromethane, and dried in vacuo. 413 mg of the titled product
6 (1:1 ratio) was obtained.

7 M.P. 125-128 °C (decomposition)

8

9 EXAMPLE 56

10 Preparation of 2-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-
11 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenoxy)acetamide
12 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-
13 benzimidazole sodium salt (382 mg) was added in dichloromethane (45 ml) and
14 triethylamine (0.1 ml). 2-[p-(chlorosulfonyl)phenoxy]acetamide(250 mg) was
15 added. The reaction mixture was stirred at room temperature overnight. The
16 reaction mixture was washed with water. Organic layer was dried over anhydrous
17 magnesium sulfate, and evaporated. Residual material was crystallized from
18 acetonitrile-ethyl ether. 437 mg of the titled product was obtained.

19 M.P. 148-153 °C (decomposition)

20 NMR (DMSO-d₆, δ): 1.93-1.97 (m, 2H), 2.18 (s, 3H), 3.35 (s, 3H), 3.46 (t, 2H),
21 4.06 (t, 2H), 4.56 (s, 2H), 4.83-5.13 (q, AB, 2H), 6.85 (d, 1H), 7.16 (d, 2H), 7.41-
22 7.60 (m, 2H), 7.79 (d, 1H), 7.89 (d, 1H), 8.00-8.02 (d, 1H), 8.16-8.18 (d, 2H)

23

24 EXAMPLE 57

25 Preparation of 1-[{2-(morpholin-4-yl)ethoxy} phenyl-4-sulfonyl]-2-[(3-methyl-4-
26 (2,2,2-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole
27 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-
28 benzimidazole (370 mg) was dissolved in 20 ml of dichloromethane and 1 ml of

1 triethylamine. [2-(Morpholin-4-yl)ethoxy]phenyl-4-sulfonyl chloride (273 mg)
2 was added and stirred at room temperature overnight. Dichloromethane layer was
3 washed with an aqueous solution composed of 0.1 M NaCl and ice-cooled 0.1 N
4 sodium bicarbonate solution. Dichloromethane layer was dried over anhydrous
5 magnesium sulfate. Solvent was removed under reduced pressure. Residual
6 material was lyophilized to provide 515 mg of the titled product.
7 NMR (CDCl₃, δ): 2.33 (s, 3H), 2.50-2.52 (m, 4H), 2.78-2.81 (t, 2H), 3.70-3.74 (m,
8 4H), 4.12-4.15 (t, 2H), 4.84-5.02 (q, AB, 2H), 6.63 (d, 1H), 6.96 (d, 2H), 7.38-7.49
9 (m, 2H), 7.81 (d, 1H), 7.99 (d, 1H), 8.04 (d, 2H), 8.26 (d, 1H)

10

11 EXAMPLE 58

12 Preparation of 1-[{2-(morpholin-4-yl)ethoxy}phenyl-4-sulfonyl]-5-methoxy-2-
13 [(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-
14 [{2-(morpholin-4-yl)ethoxy}phenyl-4-sulfonyl]-6-methoxy-2-[(3,5-dimethyl-4-
15 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

16 137 mg of [2-(Morpholin-4-yl)ethoxy]phenyl-4-sulfonyl chloride was added to
17 172 mg of 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-
18 1H-benzimidazole in dichloromethane (15 ml) and triethylamine (0.4 ml). The
19 reaction mixture was stirred at room temperature overnight. The reaction mixture
20 was washed with an aqueous solution composed of 0.1 M NaCl and 0.1 M sodium
21 bicarbonate. Organic layer was dried over anhydrous magnesium sulfate, and
22 evaporated. Residual material was lyophilized in vacuo to give 224 mg of the titled
23 product (1:1 ratio).

24 NMR (CDCl₃, δ): 2.22 (s, 3H), 2.30 (s, 3H), 2.50-2.51 (m, 4H), 2.79 (t, 2H), 3.69-
25 3.74 (m, 4H; s, 3H), 3.82 & 3.91 (2s, total 3H), 4.12 (t, 2H), 4.78-4.94 (q, AB,
26 2H), 6.93-7.08 (m, 3H), 7.46 (s, 1H), 7.68-7.86 (dd, 1H), 8.00-8.04 (m, 2H), 8.17
27 (s, 1H)

28

1 EXAMPLE 59

2 Preparation of 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-[(3-
3 methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole
4 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-
5 benzimidazole (185 mg) was dissolved in 20 ml of dichloromethane and 0.5 ml of
6 triethylamine. 2-[2-(Morpholin-4-yl)ethoxy]ethoxyphenyl-4-sulfonyl chloride (163
7 mg) was added and stirred at room temperature overnight. Dichloromethane layer
8 was washed with an aqueous solution composed of 1 M NaCl and 0.1 N NaHCO₃.
9 Dichloromethane layer was dried over anhydrous magnesium sulfate. Solvent was
10 removed under reduced pressure. Residual material was separated by preparative
11 TLC. 198 mg of the titled product was obtained.

12 NMR (CDCl₃, δ): 2.30 (s, 3H), 2.48 (m, 4H), 2.58 (t, 2H), 3.64-3.77 (m, 8H), 4.10
13 (t, 2H), 4.34-4.40 (q, 2H), 4.81-5.01 (q, AB, 2H), 6.62 (d, 1H), 6.94 (d, 2H), 7.35-
14 7.47 (m, 2H), 7.78 (d, 1H), 7.96 (d, 1H), 8.02 (d, 2H), 8.22 (d, 1H)

15

16 EXAMPLE 60

17 Preparation of 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]- 5-
18 methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-
19 benzimidazole and 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-
20 6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-
21 benzimidazole

22 162 mg of [2-{2-(morpholin-4-yl)ethoxy}ethoxy]benzene-4-sulfonyl chloride was
23 added to 172 mg of 5-Methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
24 pyridyl)methyl]sulfinyl]-1H-benzimidazole in dichloromethane (15 ml) and
25 triethylamine (0.5 ml). The reaction mixture was stirred at room temperature
26 overnight. The reaction mixture was washed with an aqueous solution composed
27 of 1 M NaCl and 0.1 M sodium bicarbonate. Organic layer was dried over
28 anhydrous magnesium sulfate, and evaporated. Residual material was dried in

1 vacuo to give 254 mg of the titled product (1:1 ratio).
2 NMR (CDCl₃, δ): 2.21 (s, 3H), 2.29 (s, 3H), 2.49-2.53 (m, 2H), 2.69-2.78 (m, 4H),
3 3.67-3.89 (m, 8H; s, 3H; s, 3H), 4.07-4.13 (m, 2H), 4.76-4.93 (q, AB, 2H), 6.92-
4 7.00 (m, 2H), 7.23 (d, 1H), 7.44 (d, 1H), 7.65-7.85 (dd, 1H), 7.98-8.03 (m, 2H),
5 8.15 (s, 1H)

6

7 EXAMPLE 61

8 Preparation of 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-
9 [[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole
10 2-[(3-Methyl-4-methoxypropoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole
11 sodium salt (191mg) was dissolved in 20 ml of dichloromethane and 0.1 ml of
12 triethylamine. 2-[2-(Morpholin-4-yl)ethoxy]ethoxyphenyl-4-sulfonyl chloride
13 (163 mg) was added and stirred at room temperature overnight. Dichloromethane
14 layer was washed with an aqueous solution composed of 1 M NaCl and 0.1 N
15 NaHCO₃. Dichloromethane layer was dried over anhydrous magnesium sulfate.
16 Solvent was removed under reduced pressure. Residual material was lyophilized to
17 give 253 mg of the titled product.

18 NMR (CDCl₃, δ): 1.99-2.03 (m, 2H), 2.21 (s, 3H), 2.46 (t, 2H), 2.55 (t, 2H), 2.67
19 (t, 2H), 3.29 (s, 3H), 3.48-3.53 (m, 2H), 3.64-3.68 (m, 6H), 3.73-3.74 (m, 2H),
20 4.02-4.07 (m, 4H), 4.74-4.97 (q, AB, 2H), 6.62 (d, 1H), 6.89-6.92 (d, 2H), 7.31-
21 7.42 (m, 2H), 7.75 (d, 1H), 7.93 (d, 1H), 8.02 (d, 2H), 8.13 (d, 1H)

22

23 EXAMPLE 62

24 Preparation of N-(carbamoylmethyl)-2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-
25 methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-
26 yl)sulfonyl]phenoxy}acetamide and N-(carbamoylmethyl)-2-{4-[(6-methoxy-2-
27 {[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-
28 yl)sulfonyl]phenoxy}acetamide

1 Method 1) 5-Methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-
2 1H-benzimidazole (172 mg) was dissolved in 20 ml of dichloromethane. Sodium
3 tert-butoxide (55 mg) and N-(carbamoylmethyl)-2-[4-
4 (chlorosulfonyl)phenoxy]acetamide (160 mg) was added. The reaction mixture
5 was stirred at 30 °C for 36 hr. The reaction mixture was filtered. The filtrate was
6 concentrated and treated with ethyl ether to give precipitates. Solid was collected,
7 and dried in vacuo. 253 mg of the titled product (1:1 ratio) was obtained.

8 Method 2) 5-Methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-
9 1H-benzimidazole (172 mg) was dissolved in 20 ml of dichloromethane and 0.4 ml
10 of triethylamine. N-(carbamoylmethyl)-2-[4-(chlorosulfonyl)phenoxy]acetamide
11 (160 mg) was added. The reaction mixture was stirred at 30 °C for 36 hr. The
12 reaction mixture was treated with additional 80 ml of dichloromethane, and
13 washed with 7% NaCl solution and 0.1 N sodium bicarbonate solution.
14 Dichloromethane layer was dried over anhydrous magnesium sulfate and
15 evaporated under reduced pressure. The residual material was lyophilized to give
16 213 mg of the titled product (1:1 ratio).

17 NMR (DMSO-d₆, δ): 2.14 (s, 3H), 2.25 (s, 3H), 3.34 (br, -NH, -NH₂), 3.66 (d,
18 2H), 3.70 (s, 3H), 3.88 (s, 3H), 4.67 (s, 2H), 4.81-5.08 (q, AB, 2H), 7.05-7.22 (m,
19 3H), 7.35 (s, 1H), 7.89 (dd, 1H), 8.14-8.18 (m, 2H), 8.32 (s, 1H)
20

21 EXAMPLE 63

22 Preparation of N-(carbamoylmethyl)-2-(4-{[2-({[3-methyl-4-(2,2,2-
23 trifluoroethoxy)-2-pyridyl]methyl}sulfinyl)benzimidazol-1-
24 yl]sulfonyl}phenoxy)acetamide

25 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-
26 benzimidazole (185 mg) was dissolved in 20 ml of dichloromethane and 0.5 ml of
27 triethylamine, and N-(carbamoylmethyl)-2-[4-(chlorosulfonyl)phenoxy]acetamide
28 (158 mg) was added. The reaction mixture was stirred at room temperature for 24

1 hr. Dichloromethane (100 ml) was added to the reaction mixture. The reaction
2 mixture was washed with saturated NaCl solution, and 0.1 N sodium bicarbonate
3 solution. Dichloromethane layer was separated and dried over anhydrous
4 magnesium sulfate. Dichloromethane was evaporated under reduced pressure to
5 give syrupy material, which was lyophilized in vacuo. 237 mg of the titled product
6 was obtained.

7 NMR (DMSO-d₆, δ): 2.23 (s, 3H), 3.36 (br, -NH₂, -NH), 3.66 (d, 2H), 4.67 (s,
8 2H), 4.84-5.17 (m, 2H and q, AB, 2H), 6.99-8.35 (m, 10H, aromatic H)

9
10 EXAMPLE 64

11 Preparation of N-(carbamoylmethyl)-2-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-
12 2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)acetamide
13 2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl)methyl]sulfinyl]-1H-
14 benzimidazole sodium salt (190 mg) was dissolved in 20 ml of dichloromethane
15 and 0.5 ml of triethylamine, and N-(carbamoylmethyl)-2-[4-
16 (chlorosulfonyl)phenoxy]acetamide (160 mg) was added. The reaction mixture
17 was stirred at room temperature for 24 hr. Dichloromethane (100 ml) was added to
18 the reaction mixture. The reaction mixture was washed with saturated NaCl
19 solution, and 0.1 N sodium bicarbonate solution. Dichloromethane layer was
20 separated and dried over anhydrous magnesium sulfate. Dichloromethane was
21 evaporated under reduced pressure to give syrupy material, which was lyophilized
22 in vacuo. 215 mg of the titled product was obtained.

23 NMR (DMSO-d₆, δ): 1.94-1.97 (m, 2H), 2.19 (s, 3H), 3.22 (s, 3H), 3.46 (t, 2H),
24 3.67 (d, 2H), 4.06 (t, 2H), 4.68 (s, 2H), 4.84-5.14 (q, AB, 2H), 6.85 (d, 1H), 7.21
25 (d, 2H), 7.42-7.55 (m, 2H), 7.80 (d, 1H), 7.91 (d, 1H), 8.02(d, 1H), 8.18(d, 2H)

26
27 EXAMPLE 65

28 Preparation of 1-[(benzotriazol-1-yl)methyl]-5-methoxy-2-[[[(3,5-dimethyl-4-

1 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[(benzotriazol-1-
2 yl)methyl]- 6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-
3 1H-benzimidazole
4 5-Methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-
5 benzimidazole (172 mg) was dissolved in 20 ml of dichloromethane. Sodium tert-
6 butoxide (55 mg) and 1-(chloromethyl)-1H-benzotriazole (85 mg) was added. The
7 reaction mixture was stirred at 30 °C for 3 days. TLC analysis (developing solvent;
8 chloroform-methanol 15:1) showed major one spot of 1-[(benzotriazol-1-
9 yl)methyl]- 5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-
10 1H-benzimidazole above 5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
11 pyridyl)methyl]sulfinyl]-1H-benzimidazole. The titled product was purified by
12 preparative thin layer chromatography. 195 mg of product, a mixture of 1-
13 [(benzotriazol-1-yl)methyl]- 5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
14 pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[(benzotriazol-1-yl)methyl]- 6-
15 methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-
16 benzimidazole was obtained (3:2 ratio).
17 NMR (CDCl₃, δ): 2.21 (s, 3H), 2.24 (s, 3H), 3.70 (s, 3H), 3.79 & 3.86 (2s, total
18 3H), 4.85-5.08 (q, AB, 2H), 6.65 (d, 2H, N-CH₂-N), 6.89-8.12 (m, 8H)
19

20 EXAMPLE 66

21 Preparation of 1-[(benzotriazol-1-yl)methyl-2-[[[(4-(3-methoxypropoxy)-3-
22 methyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole
23 2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl)methyl]sulfinyl]-1H-
24 benzimidazole sodium salt (190 mg) was dissolved in 20 ml of dichloromethane.
25 1-(Chloromethyl)-1H-benzotriazole (85 mg) was added. The reaction mixture was
26 stirred at 30 °C for 3 days. TLC analysis showed one spot of product. The reaction
27 mixture was filtered. The filtrate was concentrated under reduced pressure, and
28 treated with ethyl ether-heptane for precipitation. Precipitated solids were collected

1 and dried to give pure 1-[(benzotriazol-1-yl)methyl-2-[[[(4-(3-methoxypropoxy)-
2 3-methyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (212 mg).
3 NMR (CDCl₃, δ): 2.05-2.08 (m, 2H), 2.21 (s, 3H), 3.34 (s, 3H), 3.54 (t, 2H), 4.08
4 (t, 2H), 4.86-5.16 (q, AB, 2H), 6.69-6.70 (d, 2H, N-CH₂-N), 7.00-8.15 (m, 10H)

5
6 EXAMPLE 67

7 Preparation of diethyl [5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
8 pyridyl)methylsulfinyl]benzimidazol-1-yl]phosphate

9 5-Methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-
10 benzimidazole (172 mg) was dissolved in 50 ml of dichloromethane and 0.5 ml of
11 triethylamine. Diethyl chlorophosphate (87 mg) was added. The reaction mixture
12 was stirred at room temperature for 18 hr. The reaction mixture was washed with
13 saturated NaCl solution, and 0.1 N sodium bicarbonate solution twice times.
14 Dichloromethane layer was separated and dried over anhydrous magnesium
15 sulfate. Dichloromethane was evaporated under reduced pressure to give syrupy
16 material, 215 mg of product. Syrupy product was slowly decomposed.
17 NMR (CDCl₃, δ): 1.28-1.38 (m, 6H), 2.10 (s, 3H), 2.19(s, 3H), 3.60 (s, 3H), 3.83
18 (s, 3H), 4.20-4.28 (m, 4H), 4.72-4.87 (q, AB, 2H), 6.91 (d, 1H), 7.7 (d, 1H), 7.92
19 (s, 1H), 8.18 (s, 1H)

20

21 CHEMICAL STABILITY

22 The chemical stability of the compounds of the invention has been followed
23 kinetically at low concentration at 37 °C in a buffer solution composed of 0.2 M
24 NaCl, 50 mM sodium phosphate, pH 7.4, 2% bovine albumin serum, 5-10%
25 methanol. The compounds of Example 1 and Example 19 were measured to have
26 a half-life ($t_{1/2}$) 3 hr \pm 0.5 hr and 3.5 hr \pm 0.3 hr, respectively. The compound of
27 Example 1 has slightly higher solubility in aqueous buffer than the compound of
28 Example 19. The solubility of these compounds was found to affect their rate of

1 hydrolysis.

2 Acid stability of the compounds was assayed in 95% methanol containing 0.1 N
3 HCl. Approximately 90% of the compound of Example 1 was still present intact
4 (without decomposition) after 2.25 hour in this solution.

5 BIOLOGICAL ASSAY

6 Inhibition of ATPase activity was measured using isolated hog gastric vesicles.
7 The gastric H,K-ATPase (10 μ g) was incubated at 37 °C in a solution (1 ml)
8 composed of 0.25 M sucrose, 20 mM Pipes/Tris, pH 7.4, 0.15 M KCl, 2 mM
9 $MgCl_2$, valinomycin 2 μ g/ml, and various concentration of compounds of the
10 invention. At timed intervals, ATP was added (up to 2 mM) and incubated for 15
11 minutes and amount of released phosphate ion was measured. As a control
12 experiment the prior art drug without a labile group on the benzimidazole nitrogen
13 (*e. g.* OMEPRAZOLE or LANSOPRAZOLE) was used for measuring inhibition
14 of enzyme activity. Initially (before it underwent hydrolysis), the samples having
15 10, 20, 50, and 100 μ M of the compound of Example 1 failed to inhibit enzyme
16 activity. After 80 minutes however, the sample having 10 μ M of the compound of
17 Example 1 inhibited 10% and the sample having 50 μ M inhibited 50%. In samples
18 having 10 μ M of OMEPRAZOLE (control) and 10 μ M of the compound of
19 Example 1, the same level of inhibition was obtained after 5.75 hours of
20 hydrolysis.

21 RELATIVE PLASMA CONCENTRATION OF OMEPRAZOLE IN MALE RAT

22 Male adult rats of the Sprague-Dawley strain were used for determining the
23 concentration of OMEPRAZOLE in the plasma. All rats were deprived of food but
24 not of water for one day. Example compounds (2 mg/kg of rat weight) were orally
25 administered to male rats (weighing 250 g to 270 g) and blood samples (0.3 ml)
26 were taken at timed intervals. Blood samples were centrifuged and plasma was
27 taken out. Plasma was extracted with 0.5 ml of dichloromethane. Dichloromethane
28 layer was evaporated by nitrogen/air blowing. The residual materials were

1 dissolved in 0.5 ml of 40% acetonitrile in 10 mM phosphate buffer (pH 7.4).
2 Amounts of OMEPRAZOLE were determined by HPLC analysis. As a control,
3 OMEPRAZOLE (4 mg/kg of rat weight) was orally administrated.

4

5 TABLE 3 : Relative concentration of OMEPRAZOLE released in the plasma
6 (arbitrary unit)

| 7 min | EXAMPLE 29 | EXAMPLE 33 | EXAMPLE 37 | omeprazole |
|--------|------------|------------|------------|------------|
| 8 20 | 4.5 | 2.5 | 1.67 | 28 |
| 9 40 | 14 | 34 | 14.36 | 4 |
| 10 60 | 8.5 | 13 | 3.5 | 2 |
| 11 80 | 3.5 | 4 | 1.88 | 1 |
| 12 100 | 2.5 | 2 | 1.88 | N/D* |
| 13 120 | 1.875 | 2 | 1.5 | N/D* |
| 14 140 | 0.625 | 1.5 | 1.5 | |
| 15 160 | 0.6 | 1 | 1 | |
| 16 180 | 0.6 | 1 | 1 | |
| 17 210 | 1.5 | 1 | 0.7 | |
| 18 240 | 0.5 | 1 | 0.7 | |
| 19 270 | 0.5 | 0.5 | 0.7 | |
| 20 300 | 0.2 | 0.5 | 0.4 | |
| 21 330 | 0.1 | 0.3 | 0.2 | |
| 22 360 | 0.05 | 0.3 | 0.1 | |
| 23 390 | N/D | 0.2 | 0.1 | |
| 24 430 | | 0.1 | N/D | |

25 * N/D : non-detectable.

26

27

28 TIME COURSES OF INHIBITORY EFFECT ON GASTRIC ACID SECRETION
29 OF THE CONSCIOUS MALE RAT

30

31 Male rats (the Sprague-Dawley strain) are used. OMEPRAZOLE (2 mg) or
32 Example 33 compound (1 mg) was resuspended in 1 ml of 15% sugar and 20 mM
33 sodium phosphate buffer, pH 7.4. OMEPRAZOLE (2 mg/kg) or compound of
34 Example 33 (1 mg/kg) was orally administrated. At timed intervals (2, 3.5, and 5

1 hr), the abdomen of the rat was incised and the pylorus was ligated under light ether anesthesia. Histamine (2 mg/kg) was intravenously injected for acid stimulation. Immediately the abdomen was closed. One hour later, the stomach was removed after ligation of the esophagus. The gastric juice was collected and acid output was quantified by titration using 0.1 N NaOH solution. As a control experiment, 1 ml of 15% sugar and 20 mM phosphate buffer solution was orally administrated without any compounds (inhibitors). Acid output was quantified by same method as described above, showing maximum histamine-stimulated gastric acid secretion. Percentage inhibition was calculated from the fractional responses elicited by test compound and a control experiment. Further calculations are based on group mean responses from 3-4 rats.

12

13 TABLE 4: Inhibition of gastric acid secretion at the timed intervals

| 14 | Time course | OMEPRazole (2 | Example 33 (1 mg/kg, |
|----|-------------|---------------|----------------------|
| | | mg/kg, p.o.) | p.o.) |
| 15 | 2 hr | 90 % | 84 % |
| 16 | 3.5 hr | 46 % | 71 % |
| 17 | 5 hr | 45 % | 91 % |

18

19 The compound of Example 33 showed long duration of inhibition compared to
20 OMEPRazole. Maximum inhibition by the compound of Example 33 was
21 obtained after 5 hours, which shows that the compound of the invention is
22 continuously converted to the corresponding PPI in vivo and inhibits gastric acid
23 secretion.

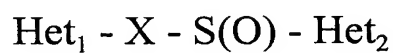
24

25

26

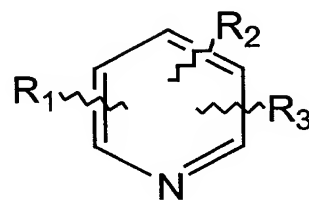
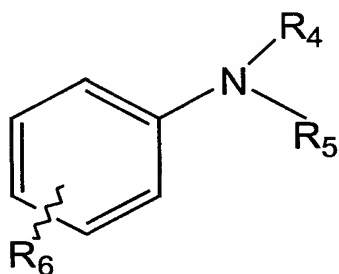
WHAT IS CLAIMED IS:

1. A compound of the formula

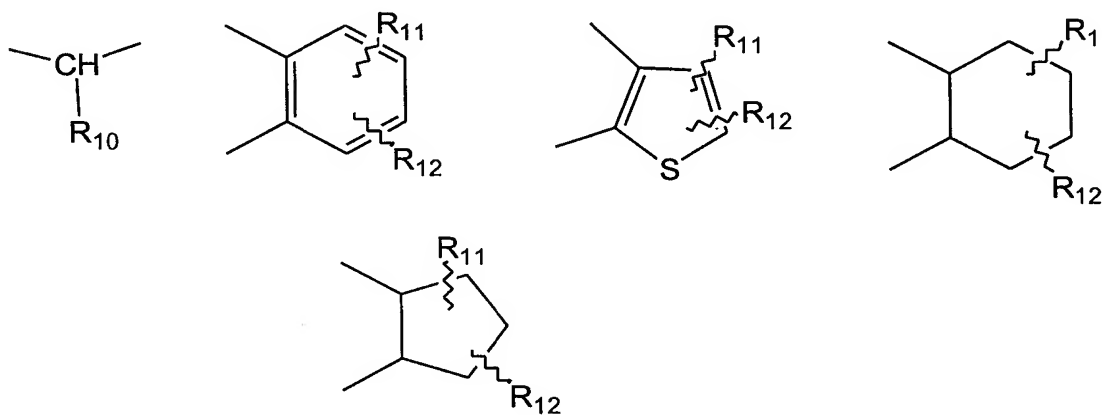


wherein

Het₁ is selected from the group consisting of the structures shown by the formulas below



X is selected from the group consisting of the structures shown by the formulas below



1 and Het₂ is selected from the group consisting of the structures shown by
2 the formulas below

3

4

5

6

7

8

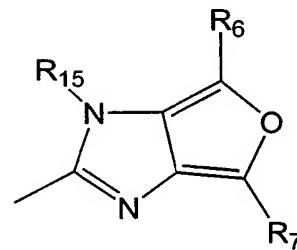
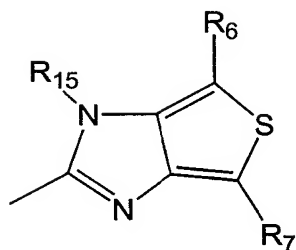
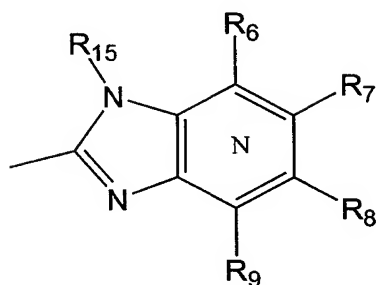
9

10

11 where N in the benzimidazole moiety represents that one of the ring carbons
12 may be exchanged for an unsubstituted N atom;

13 R₁, R₂ and R₃ are independently selected from hydrogen, alkyl of 1 to
14 10 carbons, fluoro substituted alkyl of 1 to 10 carbons, alkoxy of 1 to 10 carbons,
15 fluoro substituted alkoxy of 1 to 10 carbons, alkylthio of 1 to 10 carbons, fluoro
16 substituted alkylthio of 1 to 10 carbons, alkoxyalkoxy of 2 to 10 carbons, amino,
17 alkylamino and dialkylamino each of the alkyl groups in said alkylamino and
18 dialkyl amino groups having 1 to 10 carbons, halogen, phenyl, alkyl substituted
19 phenyl, alkoxy substituted phenyl, phenylalkoxy, each of the alkyl groups in said
20 alkyl substituted phenyl, alkoxy substituted phenyl and phenylalkoxy having 1 to
21 10 carbons, piperidino, morpholino or two of the R₁, R₂ and R₃ groups jointly
22 forming a 5 or 6 membered ring having 0 or 1 heteroatom selected from N, S and
23 O;

24 R₄ and R₅ are independently selected from hydrogen, alkyl of 1 to 10
25 carbons, fluoro substituted alkyl of 1 to 10 carbons, phenylalkyl, naphthylalkyl and
26 heteroarylalkyl, alkyl in said phenylalkyl, naphthylalkyl and heteroarylalkyl
27 groups having 1 to 10 carbons;



1 R_6 is hydrogen, halogen, alkyl of 1 to 10 carbons, fluoro substituted alkyl
 2 of 1 to 10 carbons, alkoxy having 1 to 10 carbons or fluoro substituted alkoxy
 3 having 1 to 10 carbons;

4 R_6 through R_9 are independently selected from hydrogen, alkyl of 1 to 10
 5 carbons, halogen substituted alkyl of 1 to 10 carbons, alkoxy of 1 to 10 carbons,
 6 halogen substituted alkoxy of 1 to 10 carbons, alkylcarbonyl, alkoxycarbonyl the
 7 alkyl group in said alkylcarbonyl and alkoxycarbonyl having 1 to 10 carbons,
 8 oxazolyl, imidazolyl, thiazolyl, pyrazolyl, or any two adjacent ones of the R_6
 9 through R_9 groups may form a ring that may optionally include a heteroatom
 10 selected from N, O and S and said ring may be further substituted;

11 R_{10} is hydrogen, alkyl of 1 to 10 carbons, or R_{10} may form an alkylene
 12 chain together with R_3 ,

13 R_{11} and R_{12} are independently selected from hydrogen, halogen, alkyl of
 14 1 to 10 carbons and halogen substituted alkyl of 1 to 10 carbons;

15 R_{15} is selected from the group consisting of the structures shown by the
 16 formulas below

17

18

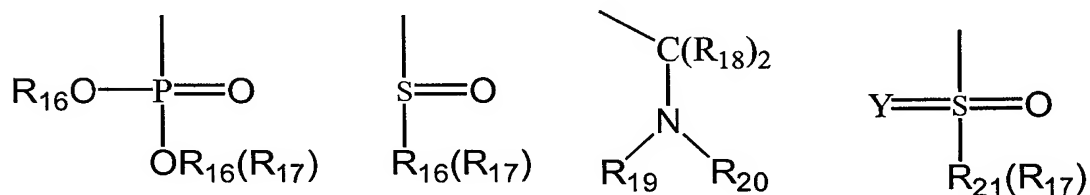
19

20

21

22

23



23 where

24 R_{16} is alkyl of 1 to 10 carbons, morpholino, piperidino, phenyl, naphthyl
 25 or heteroaryl having 1 to 3 heteroatoms selected from N, O or S, said morpholino.
 26 piperidino phenyl, naphthyl or heteroaryl groups being unsubstituted, or
 27 substituted with 1 to 5 R_{17} groups;

1 R_{17} is alkyl of 1 to 10 carbons, halogen substituted alkyl of 1 to 10
 2 carbons, alkoxy having 1 to 10 carbons, halogen substituted alkoxy of 1 to 10
 3 carbons, alkylthio having 1 to 10 carbons, halogen substituted alkylthio of 1 to 10
 4 carbons, alkoxy carbonyl having 1 to 10 carbons, halogen substituted alkoxy
 5 carbonyl having 1 to 10 carbons, F, Cl, Br, I, NO_2 , CN, OCOalkyl, NH_2 ,
 6 alkylamino and dialkylamino where in said OCOalkyl, , alkylamino and
 7 dialkylamino groups each of said alkyl group has 1 to 10 carbons, ureidoyl
 8 (RNHCONH-), guanidiny, carbamoyl, N-substituted carbamoyl, alkylcarbamoyl
 9 having 1 to 10 carbons, (alkoxycarbonyl)alkoxy groups of each of said alkoxy
 10 group has 1 to 10 carbons, (alkoxycarbonyl)alkyl groups of each of said alkoxy or
 11 alkyl group has 1 to 10 carbons, (carbamoyl)alkoxy having 1 to 10 carbons, (N-
 12 alkylcarbamoyl)alkoxy having 1 to 10 carbons, (N,N-dialkylcarbamoyl)alkoxy
 13 having 1 to 10 carbons, (N-substituted or unsubstituted carbamoyl)poly(alkoxy)
 14 having 1 to 10 carbons, (N-substituted or unsubstituted carbamoyl)alkyl having 1
 15 to 10 carbons, [N-(heteroaryl)carbamoyl]alkyl having 1 to 10 carbons, [N-
 16 (heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted
 17 heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted
 18 aryl)carbamoyl]alkoxy having 1 to 10 carbons, poly(alkoxy) group of each of said
 19 alkoxy group has 1 to 10 carbons, cyclic polyalkoxy (such as crown ether moiety),
 20 guanidiny group, ureido group, dialkylamino-poly(alkoxy) group, [N-
 21 (carbamoylalkyl)carbamoyl]alkoxy, [N-(carbamoylalkyl)carbamoyl]alkyl, [N-[[N-
 22 (heteroaryl) carbamoyl]alkyl]carbamoyl]alkoxy, [N-[[N-(substituted heteroaryl)
 23 carbamoyl]alkyl]carbamoyl]alkoxy, (sulfonato)alkyl, (sulfonato)alkoxy, N-
 24 [sulfonato)alkyl]amido, (substituted)maleimido-, (substituted)succinimido [(tri-
 25 alkyl)ammonium]-alkoxy;
 26 R_{18} is independently selected from H, alkyl of 1 to 10 carbons and phenyl;
 27 R_{19} and R_{20} are independently selected from H, alkyl of 1 to 10 carbons,
 28 halogen substituted alkyl of 1 to 10 carbons, or R_{19} and R_{20} together with the N

1 atom may form a 4 to 10 membered ring that may include one more heteroatom
 2 selected from N, O or S, said N heteroatom being unsubstituted or substituted with
 3 an alkyl group of 1 to 10 carbons, or with an aryl or heteroaryl group, and

4 R_{21} is alkyl, (aryl)alkyl, (heteroaryl)alkyl, phenyl, naphthyl or heteroaryl
 5 where heteroaryl has 1 to 3 heteroatoms independently selected from N, O and S,
 6 said phenyl, naphthyl or heteroaryl groups being unsubstituted or substituted with
 7 1 to 5 R_{17} groups,

8 Y is O or $=NR_{16}$,

9 or to a pharmaceutically acceptable salt of said compound.

10 2. A compound in accordance with Claim 1 where **Het₁** represents a
 11 substituted pyridyl group.

12 3. A compound in accordance with Claim 1 where **Het₂** represents a a
 13 susbtituted benzimidazole group.

14 4. A compound in accordance with Claim 1 where X represents a CH_2
 15 group.

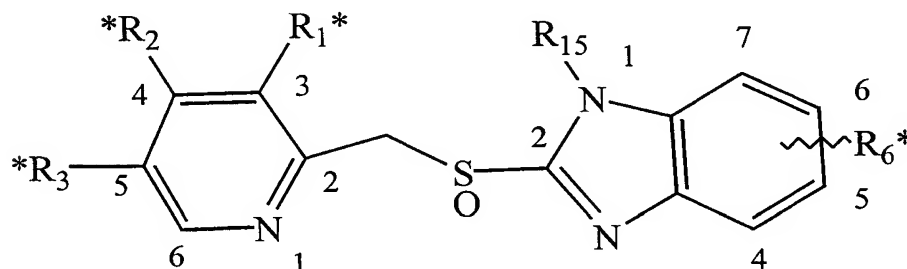
16 5. A compound in accordance with Claim 1 where R_{15} is $R_{16}(R_{17})SO-$.

17 6. A compound in accordance with Claim 1 where R_{15} is
 18 $-C(R_{18})_2-N(R_{19}R_{20})$.

19 7. A compound in accordance with Claim 1 where R_{15} is $SO_2(R_{21})(R_{17})$.

20 8. A compound in accordance with Claim 7 where R_{21} is phenyl,
 21 pyridyl, thiophenyl, thiazolyl, or imidazolyl.

22 9. A compound of the formula



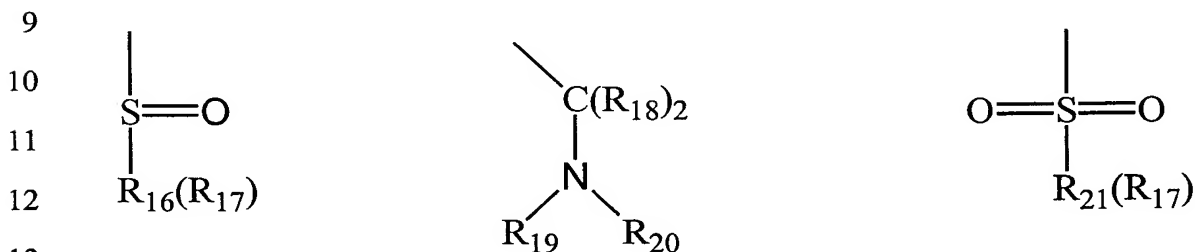
1 wherein R_6^* is H, methoxy or difluoromethoxy group in the 5 or in the 6
2 position of the benzimidazole moiety;

3 R_1^* is methyl, methoxy or chloro;

4 R_2^* is methoxy, 2,2,2-trifluoroethoxy, 4-morpholino, ethylthio or
5 (2,2,3,3,4,4,4-heptafluorobutyl)oxy;

6 R_3^* is H or methyl, and

7 R_{15} is selected from the group consisting of the structures shown by the
8 formulas below



15 where

16 R_{16} is alkyl of 1 to 10 carbons, morpholino, piperidino, phenyl, naphthyl
17 or heteroaryl having 1 to 3 heteroatoms selected from N, O or S, said morpholino.
18 piperidino phenyl, naphthyl or heteroaryl groups being unsubstituted, or
19 substituted with 1 to 5 R_{17} groups;

20 R_{17} is alkyl of 1 to 10 carbons, halogen substituted alkyl of 1 to 10
21 carbons, alkoxy having 1 to 10 carbons, halogen substituted alkoxy of 1 to 10
22 carbons, alkylthio having 1 to 10 carbons, halogen substituted alkylthio of 1 to 10
23 carbons, alkoxy carbonyl having 1 to 10 carbons, halogen substituted alkoxy
24 carbonyl having 1 to 10 carbons, F, Cl, Br, I, NO_2 , CN, OCOalkyl, NH_2 ,
25 alkylamino and dialkylamino where in said OCOalkyl, , alkylamino and
26 dialkylamino groups each of said alkyl group has 1 to 10 carbons, further R_{17} is
27 ureidoyl (RNHCONH-), guanidinyl, carbamoyl, N-substituted carbamoyl,
28 alkylcarbonyl having 1 to 10 carbons, (alkoxycarbonyl)alkoxy groups of each of

1 said alkoxy group has 1 to 10 carbons, (alkoxycarbonyl)alkyl groups of each of
2 said alkoxy or alkyl group has 1 to 10 carbons, (carbamoyl)alkoxy having 1 to 10
3 carbons, (N-alkylcarbamoyl)alkoxy having 1 to 10 carbons, (N,N-
4 dialkylcarbamoyl)alkoxy having 1 to 10 carbons, (N-substituted or unsubstituted
5 carbamoyl)poly(alkoxy) having 1 to 10 carbons, (N-substituted or unsubstituted
6 carbamoyl)alkyl having 1 to 10 carbons, [N-(heteroaryl)carbamoyl]alkyl having 1
7 to 10 carbons, [N-(heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-
8 (substituted heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted
9 aryl)carbamoyl]alkoxy having 1 to 10 carbons, poly(alkoxy) group of each of said
10 alkoxy group has 1 to 10 carbons, cyclic polyalkoxy (such as crown ether moiety),
11 guanidinyll group, ureido group, dialkylamino-poly(alkoxy) group, [N-
12 (carbamoylalkyl)carbamoyl]alkoxy, [N-(carbamoylalkyl)carbamoyl]alkyl, [N-[[N-
13 (heteroaryl) carbamoyl]alkyl]carbamoyl]alkoxy, [N-[[N-(substituted heteroaryl)
14 carbamoyl]alkyl]carbamoyl]alkoxy, [(tri-alkyl)ammonium]-alkoxy,
15 (sulfonato)alkyl, (sulfonato)alkoxy, N-[sulfonato)alkyl]amido,
16 (substituted)maleimido-, (substituted)succinimido;

17 R_{18} is independently selected from H, alkyl of 1 to 10 carbons and phenyl;

18 R_{19} and R_{20} are independently selected from H, alkyl of 1 to 10 carbons,
19 halogen substituted alkyl of 1 to 10 carbons, or R_{19} and R_{20} together with the N
20 atom may form a 4 to 10 membered ring that may include one more heteroatom
21 selected from N, O or S, said N heteroatom being unsubstituted or substituted with
22 an alkyl group of 1 to 10 carbons, or with an aryl or heteroaryl group, and

23 R_{21} is alkyl, (aryl)alkyl, (heteroaryl)alkyl, phenyl, naphthyl or heteroaryl
24 having 1 to 3 heteroatoms independently selected from N, O and S, said phenyl,
25 naphthyl or heteroaryl groups being unsubstituted or substituted with 1 to 5 R_{17}
26 groups,

27 or to a pharmaceutically acceptable salt of said compound.

28 **10.** A compound in accordance with Claim 9 where R_{15} is $R_{16}(R_{17})SO-$.

1 **11.** A compound in accordance with Claim 10 where $R_{16}(R_{17})$ phenyl,
2 substituted or unsubstituted with the R_{17} group.

3 **12.** A compound in accordance with Claim 11 where R_{17} is selected
4 from Cl, Br, F, lower alkyl, lower alkoxy, trifluoromethyl, trifluoromethoxy, di-
5 (lower alkyl)amino, and lower alkoxycarbonyl.

6 **13.** A compound in accordance with Claim 11 where R_{16} is unsubstituted
7 or where R_{17} is selected from Cl, Br, F, methyl, methoxy, trifluoromethyl,
8 trifluoromethoxy, dimethylamino and ethoxycarbonyl.

9 **14.** A compound in accordance with Claim 9 where R_{15} is
10 $R_{19}R_{20}N-C(R_{18})_2$.

11 **15.** A compound in accordance with Claim 14 where R_{18} is H or lower
12 alkyl, and $R_{19}R_{20}N$ represents di-(lower alkyl)amino, *N*-succinimidyl, *N*-
13 morpholinyl, *N*-piperidinyl, *N*-(*N*-4-methyl)hexahydropyrazinyl, *N*,*N*-
14 phenyl,methyl-amino, *N*-tetrahydropyrrolyl or *N*-(benzotriazol-1-yl).

15 **16.** A compound in accordance with Claim 15 where $R_{19}R_{20}N$ represents
16 dimethylamino, *N*-morpholino, and *N*-piperidinyl.

17 **17.** A compound in accordance with Claim 9 where R_{15} is $R_{21}(R_{17})SO_2$.

18 **18.** A compound in accordance with Claim 17 where $R_{21}(R_{17})$ is phenyl,
19 thienyl or pyridyl, substituted or unsubstituted with the R_{17} group.

20 **19.** A compound in accordance with Claim 18 where R_{17} is selected
21 from Cl, Br, F, lower alkyl, lower alkoxy, trifluoromethyl, trifluoromethoxy, di-
22 (lower alkyl)amino, lower alkoxycarbonyl, carbamoyl, guanidinyl, ureidoyl,
23 (carbamoyl)alkoxy, [N-(heteroaryl)carbamoyl]alkoxy, morpholinyl, (morpholin-
24 4-yl)alkoxy, [(morpholin-4-yl)alkoxy]alkoxy, (di-(lower alkyl)amino)alkoxy, [N-
25 [(carbamoyl) alkyl]carbamoyl]alkoxy, poly(alkoxy), sodium(sulfonato)alkoxy,
26 (trimethylammonium)alkoxy, and cyclic tetra- or penta-ethyleneoxy.

27 **20.** A compound in accordance with Claim 18 R_{21} is unsubstituted or
28 where R_{17} is selected from Cl, Br, F, lower alkyl, lower alkoxy, trifluoromethyl,

1 di-(lower alkyl)amino, lower alkoxycarbonyl, carbamoyl, guanidiny, ureido,yl,
2 (carbamoyl)methoxy, [N-(pyridyl)carbamoyl]methoxy, morpholinyl, (morpholin-
3 4-yl)alkoxy, [(morpholin-4-yl)alkoxy]alkoxy, 2-(dimethylamino)ethoxy, [N-
4 [(carbamoyl) methyl]carbamoyl]methoxy, poly(alkoxy), and cyclic tetra- or penta-
5 ethyleneoxy group.

6 **21.** A compound in accordance with Claim 9, selected from the group
7 consisting of:

8 1-benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
9 pyridyl)methylsulfinyl]-1H-benzimidazole,
10 1-benzenesulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
11 pyridyl)methylsulfinyl]-1H-benzimidazole,
12 1-benzenesulfonyl-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
13 pyridyl)methylsulfinyl]-1H-benzimidazole,
14 1-benzenesulfonyl-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
15 pyridyl)methylsulfinyl]-1H-benzimidazole,
16 1-benzenesulfonyl-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
17 pyridyl)methylsulfinyl]-1H-benzimidazole,
18 1-(p-chlorobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
19 pyridyl)methylsulfinyl]-1H-benzimidazole,
20 1-(p-chlorobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
21 pyridyl)methylsulfinyl]-1H-benzimidazole,
22 1-(p-chlorobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
23 pyridyl)methylsulfinyl]-1H-benzimidazole,
24 1-(p-chlorobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
25 pyridyl)methylsulfinyl]-1H-benzimidazole,
26 1-(p-chlorobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
27 pyridyl)methylsulfinyl]-1H-benzimidazole,
28 1-(p-bromobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

- 1 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 2 1-(p-bromobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 3 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 4 1-(p-bromobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 5 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 6 1-(p-bromobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 7 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 8 1-(p-bromobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 9 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 10 1-(p-fluorobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 11 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 12 1-(p-fluorobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 13 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 14 1-(p-fluorobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 15 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 16 1-(p-fluorobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 17 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 18 1-(p-fluorobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 19 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 20 1-(p-methylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 21 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 22 1-(p-methylbenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 23 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 24 1-(p-methylbenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 25 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 26 1-(p-methylbenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 27 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 28 1-(p-methylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-

- 1 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 2 1-(p-methoxybenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 3 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 4 1-(p-methoxybenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 5 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 6 1-(p-methoxybenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 7 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 8 1-(p-methoxybenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 9 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 10 1-(p-methoxybenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 11 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 12 1-(3-trifluoromethylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 13 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 14 1-(3-trifluoromethylbenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 15 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 16 1-(3-trifluoromethylbenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 17 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 18 1-(3-trifluoromethylbenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 19 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 20 1-(3-trifluoromethylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 21 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 22 1-(p-trifluoromethoxybenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 23 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 24 1-(p-trifluoromethoxybenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 25 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 26 1-(p-trifluoromethoxybenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 27 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 28 1-(p-trifluoromethoxybenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-

- 1 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 2 1-(p-trifluoromethoxybenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 3 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 4 1-(p-dimethylaminobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 5 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 6 1-(p-dimethylaminobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-
- 7 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 8 1-(p-dimethylaminobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 9 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 10 1-(p-ethoxycarbonylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 11 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 12 1-(p-ethoxycarbonylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-
- 13 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 14 1-(pyridine-3-sulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 15 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 16 1-(pyridine-3-sulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 17 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 18 1-(pyridine-3-sulfonyl)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 19 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 20 1-(pyridine-3-sulfonyl)-5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
- 21 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 22 1-(pyridine-3-sulfonyl)-6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
- 23 pyridyl)methylsulfinyl]-1H-benzimidazole,
- 24 1-[4-[(morpholin-4-yl)phenyl]sulfonyl]-5-methoxy-2-[(3,5-dimethyl-4-methoxy-
- 25 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 26 1-[4-[(morpholin-4-yl)phenyl]sulfonyl]-6-methoxy-2-[(3,5-dimethyl-4-methoxy-
- 27 2-pyridyl)methylsulfinyl]-1H-benzimidazole,
- 28 N-[4-[[5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

- 1 pyridyl)methyl]sulfinyl]benzimidazol-1-yl)sulfonyl]phenyl]urea,
- 2 N-[4-[[6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
- 3 pyridyl)methyl]sulfinyl]benzimidazol-1-yl)sulfonyl]phenyl]urea,
- 4 N-(4-{[2-([3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 5 pyridyl)methyl}sulfinyl]benzimidazol-1-yl)sulfonyl}phenyl)urea,
- 6 N-(4-{[2-([4-(3-methoxypropoxy)-3-methyl-2-
- 7 pyridyl)methyl}sulfinyl]benzimidazol-1-yl)sulfonyl}phenyl)urea,
- 8 N-(4-{[2-[[[(3,4-di(methoxy)-2-pyridyl)methyl]sulfinyl]-5-(difluoromethoxy)-
- 9 benzimidazol-1-yl)sulfonyl}phenyl)urea,
- 10 N-(4-{[2-[[[(3,4-di(methoxy)-2-pyridyl)methyl]sulfinyl]-6-(difluoromethoxy)-
- 11 benzimidazol-1-yl)sulfonyl}phenyl)urea,
- 12 15-{[2-([4-(3-methoxypropoxy-3-methyl-2-
- 13 pyridyl)methyl}sulfinyl]benzimidazol-1-yl)sulfonyl}-
- 14 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
- 15 15-{[2-([3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 16 pyridyl)methyl}sulfinyl]benzimidazol-1-yl)sulfonyl}-
- 17 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
- 18 15-[(5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-
- 19 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]-
- 20 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
- 21 15-[(6-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-
- 22 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]-
- 23 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
- 24 15-[(5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-
- 25 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]-
- 26 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
- 27 15-[(6-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-
- 28 pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]-

- 1 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
- 2 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
- 3 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
- 4 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
- 5 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
- 6 pyridyl)acetamide,
- 7 N-(carbamoylmethyl)-2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
- 8 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
- 9 2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
- 10 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
- 11 2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
- 12 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
- 13 pyridyl)acetamide,
- 14 N-(carbamoylmethyl)-2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
- 15 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
- 16 2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 17 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenoxy)acetamide,
- 18 2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 19 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenoxy)-N-(2-
- 20 pyridyl)acetamide,
- 21 N-(carbamoylmethyl)-2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 22 pyridyl]methyl} sulfinyl)benzimidazol-1-yl]sulfonyl} phenoxy)acetamide,
- 23 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-
- 24 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
- 25 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-
- 26 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
- 27 pyridyl)acetamide,
- 28 N-(carbamoylmethyl)-2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-

- 1 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
2 2-{4-[(6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
3 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
4 2-{4-[(6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
5 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
6 pyridyl)acetamide,
7 N-(carbamoylmethyl)-2-{4-[(6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
8 pyridyl)methyl]sulfinyl} benzimidazol-1-yl)sulfonyl]phenoxy} acetamide,
9 2-(4-{2-([4-(3-methoxypropoxy)-3-methyl-2-
10 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl} phenoxy)acetamide,
11 2-(4-{2-([4-(3-methoxypropoxy)-3-methyl-2-
12 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl} phenoxy)-N-(2-
13 pyridyl)acetamide,
14 N-(carbamoylmethyl)-2-(4-{2-([4-(3-methoxypropoxy)-3-methyl-2-
15 pyridyl]methyl} sulfinyl)benzimidazol-1-yl)sulfonyl} phenoxy)acetamide,
16 1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-5-(difluoromethoxy)-2-
17 [[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
18 1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-6-(difluoromethoxy)-2-
19 [[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
20 1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-5-methoxy-2-[(3,5-
21 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
22 1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-6-methoxy-2-[(3,5-
23 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
24 1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-2-[(3-methyl-4-
25 methoxypropoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
26 1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-2-[(3-methyl-4-(2,2,2-
27 trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
28 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[[[(4-(3-methoxypropoxy)-3-

- 1 methyl-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 2 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-5-(difluoromethoxy)-2-[(3,4-
- 3 dimethoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 4 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-5-methoxy-2-[(3,5-dimethyl-4-
- 5 methoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 6 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-6-(difluoromethoxy)-2-[(3,4-
- 7 dimethoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 8 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-6-methoxy-2-[(3,5-dimethyl-4-
- 9 methoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 10 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[[[3-methyl-4-(2,2,2-
- 11 trifluoroethoxy)-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 12 1-[(N,N-dimethylamino)methyl]benzene-4-sulfonyl]-5-methoxy-2-[(3,5-
- 13 dimethyl-4-methoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 14 1-[2-acetamido-4-methyl-5-thiazolylsulfonyl]-5-methoxy-2-[(3,5-dimethyl-4-
- 15 methoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 16 1-(thiophene-2-sulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 17 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 18 1-[(N,N-dimethylamino)methyl]benzene-4-sulfonyl]-6-methoxy-2-[(3,5-
- 19 dimethyl-4-methoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 20 1-[2-acetamido-4-methyl-5-thiazolylsulfonyl]-6-methoxy-2-[(3,5-dimethyl-4-
- 21 methoxy-2-pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 22 1-(thiophene-2-sulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-
- 23 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 24 1-(thiophene-2-sulfonyl)-2-[[[4-(3-methoxypropoxy)-3-methyl-2-
- 25 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 26 1-(thiophene-2-sulfonyl)-5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-
- 27 pyridyl)methyl)sulfinyl]-1H-benzimidazole,
- 28 1-(thiophene-2-sulfonyl)-6-(difluoromethoxy)-2-[(3,4-dimethoxy-2-

- 1 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 2 1-(thiophene-2-sulfonyl)-]- 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
- 3 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 4 1-(phenylmethylsulfonyl)-5-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 5 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 6 1-(n-propanesulfonyl)-5-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 7 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 8 1-(n-butanesulfonyl)-5-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 9 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 10 1-(isopropylsulfonyl)-5-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 11 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 12 1-[(N,N-dimethylamino)benzene-4-sulfonyl]-5-methoxy-2-[[[3,5-dimethyl-4-
- 13 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 14 1-(phenylmethylsulfonyl)-6-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 15 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 16 1-(n-propanesulfonyl)-6-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 17 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 18 1-(n-butanesulfonyl)-6-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 19 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 20 1-(isopropylsulfonyl)-6-methoxy-2-[[[3,5-dimethyl-4-methoxy-2-
- 21 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 22 1-[(N,N-dimethylamino)benzene-4-sulfonyl]-6-methoxy-2-[[[3,5-dimethyl-4-
- 23 methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 24 1-(pyridine-3-sulfonyl)-2-[[[3-methyl-4-methoxypropoxy-2-
- 25 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 26 1-[4-(morpholin-4-yl)phenylsulfonyl]-2-[[[4-(3-methoxypropoxy)-3-methyl-2-
- 27 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 28 1-benzenesulfonyl-2-[[[3-chloro-4-morpholino-2-pyridyl)methyl]sulfinyl]-5-

- 1 methoxy-(1H)-benzimidazole,
- 2 1-benzenesulfonyl-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-
- 3 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 4 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]-1H-benzimidazole,
- 5 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[5,4-c]pyridine,
- 6 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[4,5-c]pyridine,
- 7 1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]-5-nitro-benzimidazole,
- 8 1-benzenesulfonyl-2-[{2-(dimethylamino)phenyl}methylsulfinyl]-1H-
- 9 benzimidazole,
- 10 1-benzenesulfonyl-2-[[[4-(2,2,3,3,4,4,4-heptafluorobutyl)oxy]-2-
- 11 pyridyl)methyl]sulfinyl]-1H-thieno[3,4-d]imidazole,
- 12 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[(3-
- 13 methoxyphenyl)methylsulfinyl]imidazolo{5,4-c}pyridine,
- 14 1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[{2-
- 15 (dimethylamino)phenyl}methylsulfinyl]-1H-benzimidazole,
- 16 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-5-methoxy-2-[[{(3,5-
- 17 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 18 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-6-methoxy-2-[[{(3,5-
- 19 dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 20 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-[[[(4-(3-
- 21 methoxypropoxy)-3-methyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 22 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-5-(difluoromethoxy)-
- 23 2-[[{(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 24 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-6-(difluoromethoxy)-
- 25 2-[[{(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 26 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-[[[3-methyl-4-
- 27 (2,2,2-trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
- 28 1-(benzotriazol-1-yl)methyl-5-methoxy-2-[[{(3,5-dimethyl-4-methoxy-2-

1 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
2 1-(benzotriazol-1-yl)methyl-6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
3 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
4 1-(benzotriazol-1-yl)methyl-2-[[[4-(3-methoxypropoxy)-3-methyl-2-
5 pyridyl]methyl]sulfinyl]-1H-benzimidazole,
6 diethyl [5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
7 pyridyl)methyl]sulfinyl]benzimidazol-1-yl]phosphate,
8 1-(4-acetaminobenzenesulfonyl)-5-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
9 pyridyl)methyl]sulfinyl]-1H-benzimidazole,
10 1-(4-acetaminobenzenesulfonyl)-6-methoxy-2-[[[(3,5-dimethyl-4-methoxy-2-
11 pyridyl)methyl]sulfinyl]-1H-benzimidazole,

12 **22.** A pharmaceutical composition comprising a pharmaceutically
13 acceptable excipient and a prodrug of a proton pump inhibitor in accordance with
14 Claim 1.

15 **23.** A pharmaceutical composition comprising a pharmaceutically
16 acceptable excipient and a prodrug of a proton pump inhibitor in accordance with
17 Claim 9.

18 **24.** A pharmaceutical composition comprising a pharmaceutically
19 acceptable excipient and a prodrug of a proton pump inhibitor in accordance with
20 Claim 21.

21 **25.** A pharmaceutical composition in accordance with Claim 22, 23 or
22 24, said composition comprising a liquid adapted for injection to a mammal, said
23 liquid having a pH not exceeding 8.5 pH units.

24 **26.** A compound in accordance with Claim 1 where Het₁ is m-
25 methoxyphenyl.

26

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 99/18048

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/12 C07D401/14 C07D409/14 C07D417/14 C07D235/28
 C07D471/04 A61K31/4184 A61K31/4439

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | EP 0 045 200 A (UPJOHN CO) 3 February 1982 (1982-02-03) page 22, line 28; claims 1,7,9 | 1,22-25 |
| X | GB 2 134 523 A (HAESSE AB) 15 August 1984 (1984-08-15) page 18, line 3; claims 1,19; example 134; table 1 | 1,22-25 |
| A | US 4 686 230 A (RAINER GEORG ET AL) 11 August 1987 (1987-08-11) cited in the application claims 1,21; examples | 1,22-25 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

21 December 1999

Date of mailing of the international search report

11/01/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3018

Authorized officer

Bosma, P

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/18048

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| EP 0045200 A | 03-02-1982 | US 4359465 A | 16-11-1982 |
| | | DE 3176664 A | 07-04-1988 |
| | | JP 1060008 B | 20-12-1989 |
| | | JP 1574094 C | 20-08-1990 |
| | | JP 57053406 A | 30-03-1982 |
| GB 2134523 A | 15-08-1984 | AT 386825 B | 25-10-1988 |
| | | AT 43584 A | 15-03-1988 |
| | | AU 578891 B | 10-11-1988 |
| | | AU 2445684 A | 16-08-1984 |
| | | BE 898880 A | 10-08-1984 |
| | | CH 666892 A | 31-08-1988 |
| | | CY 1555 A | 22-03-1991 |
| | | DE 3404610 A | 16-08-1984 |
| | | DK 59184 A | 12-08-1984 |
| | | FI 840547 A | 12-08-1984 |
| | | FR 2543551 A | 05-10-1984 |
| | | GB 2174988 A, B | 19-11-1986 |
| | | IT 1177553 B | 26-08-1987 |
| | | JP 59181277 A | 15-10-1984 |
| | | LU 85209 A | 12-09-1985 |
| | | NL 8400446 A | 03-09-1984 |
| | | NO 840504 A | 13-08-1984 |
| | | NO 882001 A | 13-08-1984 |
| | | NZ 207102 A | 30-09-1987 |
| | | SE 8400688 A | 12-08-1984 |
| | | SE 8700498 A | 10-02-1987 |
| | | SE 8700499 A | 10-02-1987 |
| | | US 5039806 A | 13-08-1991 |
| | | ZA 8401011 A | 26-09-1984 |
| US 4686230 A | 11-08-1987 | AT 79377 T | 15-08-1992 |
| | | AU 5198886 A | 15-05-1986 |
| | | DE 3586498 A | 17-09-1992 |
| | | DK 308986 A | 27-06-1986 |
| | | WO 8602646 A | 09-05-1986 |
| | | EP 0201575 A | 20-11-1986 |
| | | ES 548455 A | 16-04-1987 |
| | | FI 862720 A | 25-06-1986 |
| | | GR 852631 A | 03-02-1986 |
| | | HU 40643 A | 28-01-1987 |
| | | IL 76839 A | 31-08-1988 |
| | | JP 7005588 B | 25-01-1995 |
| | | JP 62500664 T | 19-03-1987 |
| | | NO 862618 A | 21-08-1986 |
| | | NZ 214005 A | 27-10-1989 |
| | | PT 81396 A, B | 01-11-1985 |